HAEMATO-BIOCHEMICAL PARAMETERS OF WOMEN PRESENTING WITH PRIMARY POSTPARTUM HAEMORRHAGE (PPH) AT THE KOMFO ANOKYE TEACHING HOSPITAL

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DECLARATION

The experimental work described in this thesis was carried out at the Department of Molecular Medicine, KNUST. This work has not been submitted for any other degree.

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ABSTRACT

Introduction: Among the various causes of maternal mortality, Postpartum Haemorrhage (PPH) has historically been and remains the single most important factor. The current study sought to identify certain antepartum parameters which may be associated with primary PPH and may have utility for screening and clinical management among women. It also sought to evaluate visual estimation as a method of diagnosis of primary PPH.

Methods: This nested case-control study consisted of 345 women at term, recruited at random from the KATH, O & G department, Kumasi from April to October 2012. 55 women developed primary PPH after vaginal delivery (cases), 216 women, after vaginal delivery did not develop primary PPH (controls) and 74 went through cesarean section (excluded). A questionnaire was administered to gather information on demography, anthropometry, clinical and obstetric history. Blood samples were taken for haematological and biochemical studies.

***Results*:** Prevalence of primary PPH was 15.8%. Visual estimation (250mls), upon comparison with direct measurement (306mls) underestimated blood loss by about 56mls and thus primary PPH by about 3.5%. Univariate analysis showed AST (P=0.043), ALB (P=0.001), URE (P<0.001), CRE (P=0.002), URE/CRE ratio (P=0.014), HGB/anaemia (P<0.001), ABO blood type (P=0.002), HCT (P<0.001), WBC (P=0.023), ESR (P=0.018) and Blood film picture (P<0.001) to be associated with primary PPH. After adjustment by multivariate analysis five factors remained significant. Increasing CRE, incresing URE/CRE ratio and decreasing HGB (<10g/dL) were associated with a higher likelihood of dveloping primaryPPH. Non-O blood groups (A nd B positive) were associated with a less likelihood of developing primary PPH.

Conclusion: Many antepartum and laboratory parameters are associated with primary PPH but only a few have screening utility. We however conclude that a total clinical work-up, including a laboratory evaluation of the independent variables identified in this study could help a great deal in identifying individuals at high risk. Visual estimation of blood loss after vaginal delivery is unreliable and has a huge tendency to underestimate primary PPH and its consequences.

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TABLE OF CONTENTS

DECLARATION ..... **I**

ABSTRACT ..... **II**

ACKNOWLEDGEMENT ..... **IV**

TABLE OF CONTENTS ..... **V**

LIST OF TABLES ..... **VIII**

LIST OF FIGURES ..... **IX**

ABBREVIATIONS ..... **X**

Chapter 1 **INTRODUCTION** **1**

1.1 GENERAL INTRODUCTION 1
1.2 STUDY HYPOTHESIS 2
1.3 JUSTIFICATION 3
1.4 MAIN OBJECTIVE/AIM 4
1.4.1 Specific objectives *4*

Chapter 2 **LITERATURE REVIEW** **5**

2.1 POSTPARTUM HAEMORRHAGE (PPH) 5
2.2 CHALLENGES ASSOCIATED WITH DEFINITION AND DIAGNOSIS 6
2.3 DETERMINING BLOOD LOSS IN PRIMARY PPH: VISUAL ESTIMATION VERSUS CALIBRATED MEASUREMENT 7
2.4 SCALE OF THE PROBLEM 8
2.4.1 PPH in the world *8*
2.4.2 PPH in Africa *9*
2.4.3 PPH in Ghana *10*
2.5 THE FEMALE REPRODUCTIVE SYSTEM 11
2.5.1 The Uterine tubes *11*
2.5.2 The Uterus *12*
2.5.3 Uterine wall *12*
2.5.4 Blood supply *13*
2.5.5 Vagina *14*
2.5.6 Vulva (Pudendum) *14*
2.6 CHANGES IN PREGNANCY 15
2.6.1 Digestive system, nutrition, and metabolism *15*
2.6.2 Circulatory system *16*
2.6.3 Respiratory system *17*
2.6.4 Urinary system *17*
2.6.5 Integumentary system *18*
2.6.6 Coagulation and fibrinolysis *18*
2.7 CHILDBIRTH 19
2.7.1 Uterine contractility *19*
2.7.2 Labour contractions *20*
2.7.3 Stages of labour *20*
2.7.3.1 First stage (Dilation) 21
2.7.3.2 Second stage (Expulsion) 21
2.7.3.3 Third stage (Placental) 21
2.7.3.4 Fourth stage ("immediate postpartum") 23
2.8 CAUSES OF PPH 23
2.8.1 Tone *24*

2.8.2 Trauma ... *25*
2.8.3 Tissue ... *25*
2.8.4 Thrombin ... *25*
2.9 ANTENATAL RISK FACTORS FOR PPH ... 26
2.10 COMPLICATIONS OF PPH ... 28
2.11 PPH PREVENTION ... 29
2.12 BLEEDING AND COAGULATION ... 30
2.12.1 Platelets ... *31*
2.12.2 Coagulation ... *31*
2.12.3 Tests of Haemostasis ... *34*
2.13 THE LIVER AND ITS ROLE IN HAEMOASTASIS ... 34
2.13.1 Haemostatic abnormalities in liver disease ... *35*
2.13.2 Thrombocytopenia ... *38*
2.13.3 Disseminated Intravascular Coagulation (DIC) ... *38*
2.13.4 Laboratory findings for coagulation in liver disease ... *39*
2.14 THE KIDNEYS ... 39
2.14.1 Haemostatic disorders in kidney disease ... *40*
2.15 ANAEMIA ... 41
2.15.1 Signs and symptoms ... *41*
2.15.2 Diagnosis ... *42*
2.15.3 Grading of anaemia ... *42*
2.15.4 Anaemia and pregnancy ... *42*

Chapter 3 **MATERIALS AND METHODS ... 44**

3.1 STUDY DESIGN ... 44
3.2 RECRUITMENT OF PARTICIPANTS ... 45
3.3 ADMINISTRATION OF QUESTIONNAIRES ... 46
3.4 MEASUREMENT OF ANTHROPOMETRIC VARIABLES ... 47
3.5 MEASUREMENT OF VITAL SIGNS ... 48
3.5.1 Blood pressure ... *48*
3.5.2 Temperature ... *48*
3.5.3 Pulse ... *48*
3.6 SAMPLE COLLECTION AND PREPARATION ... 49
3.7 BIOCHEMICAL ASSAYS ... 50
3.7.1 Total protein (Biuret) ... *50*
3.7.2 Albumin (BCG) ... *50*
3.7.3 Aspartate aminotransferase (AST) ... *51*
3.7.4 Alanine aminotransferase (ALT) ... *51*
3.7.5 Globulins ... *51*
3.7.6 Urea ... *52*
3.7.7 Creatinine ... *52*
3.8 COAGULATION STUDIES ... 53
3.8.1 Prothrombin Time (PT) ... *53*
3.8.2 Activated Partial Thromboplastin Time (APTT) ... *54*
3.9 HAEMATOLOGICAL PARAMETERS ... 54
3.9.1 Full/Complete blood count (FBC) ... *54*
3.9.2 The Erythrocyte Sedimentation Rate (ESR) ... *55*
3.9.3 Glucose-6-Phosphate Dehydrogenase (G6PD) ... *55*
3.9.4 Sickle cell slide test ... *56*
3.9.5 ABO blood group and Rh "D" status ... *57*
3.9.6 Blood film (Thick and thin) ... *57*
3.10 CUT OFFS AND REFERENCE INTERVALS ... 57
3.11 DIAGNOSTIC CRITERIA AND DEFINITION ... 58
3.11.1 Measurement of blood loss ... *58*
3.12 STATISTICAL ANALYSIS ... 58

Chapter 4 **RESULTS ... 60**

Chapter 5 **DISCUSSION** **73**

5.1 PREVALENCE OF PRIMARY PPH 73
5.2 ETHNICITY AND PRIMARY PPH 75
5.3 OBSTETRIC HISTORY AND PRIMARY PPH 75
5.4 BMI AND PRIMARY PPH 76
5.5 BIOCHEMICAL PARAMETERS AND PRIMARY PPH 77
5.6 COAGULOPATHY AND PRIMARY PPH 79
5.7 HAEMATOLOGICAL PARAMETERS AND PRIMARY PPH 80
5.8 DIAGNOSIS OF PRIMARY PPH: ACCURACY OF BLOOD LOSS ESTIMATION 81

Chapter 6 **CONCLUSIONS** **83**

6.1 CONCLUSION 83
6.2 RECOMMENDATIONS 84

REFERENCES **85**

LIST OF TABLES

Table 2.1 Prevalence of PPH in Ghana over a five-year period. 10
Table 2.2 Causes of PPH 24
Table 2.3 Comparison of active and expectant management of labour. 30
Table 2.4 Families of coagulation proteins. 33
Table 2.5 Typical Results in haemostasis disorders. 34
Table 4.1 Socio-demographic parameters of study participants. 60
Table 4.2 Clinical and obstetric history of study participants. 61
Table 4.3 Anthropometric variables of study participants. 64
Table 4.4 Biochemical and coagulation parameters of study participants. 65
Table 4.5 Haematological parameters of study population. 67
Table 4.6 Comparison of direct calibrated measurement to visual estimation as measures of blood loss during delivery. 70
Table 4.7 Multivariate logistic regression for independent variables. 71

LIST OF FIGURES

Figure 1-1 Causes of maternal mortality in Africa. 1
Figure 2-1 Schematic presentation of the coagulation cascade. 33
Figure 3-1 Schematic representation of study design and recruitment process 46
Figure 3-2 Measurement of waist to hip ratio in different body sizes. 47

ABBREVIATIONS

ALB- Albumin

ALT- Alanine aminotransferase

AMTSL-Active Management of Third Stage of Labour

APTT- Activated Partial Thromboplastin Time

AST- Aspartate Aminotransferase

BASO- Basophil

BMI- Body Mass Index

Ca- Calcium

CBC- Complete Blood Count

Cm- Centimetres

CRE- Creatinine

DIC- Disseminated Intravascular Coagulation

eGFR- Estimated Glomerular Filtration Rate

EO- Eosinophil

ESLD- End Stage Liver Disease

ESR-Erythrocyte Sedimentation Rate

FDP- Fibrin Degradation products

FII, FIII, FIV etc.- Factor 2, Factor 3, Factor 4, etc.

G6PD- Glucose-6-Phosphate Dehydrogenase

GNA- Ghana News Agency

HCT- Haematocrit

HGB- Haemoglobin

HMWK- High Molecular Weight Kininogen

hr- Hour

INR-International Normalised Ratio

ITP- Idiopathic Thrombocytopenic Purpura

JHS- Junior High School

Kal- Kallikrein

KATH- Komfo Anokye Teaching Hospital

Kg- Kilogram

LDL- Low Density Lipoprotein

LYMPH-Lymphocyte

MCH- Mean Cell Haemoglobin

MCHC- Mean Corpuscular Haemoglobin Concentration

MCV- Mean Cell Volume

MDG- Millennium Development Goals

ml- Millilitres

MOH- Ministry of Health

MONO-Monocyte

NEUT- Neutrophil

NIDDK- National Institute of Diabetes, Digestion and Kidney diseases

NSW- New South Whales

OR- Odds Ratio

OT- Oxytocin

O & G – Obstetrics and Gynaecology

PAI-1- Plasminogen Activator Inhibitor 1

PAIgG- Platelet Associated Immunoglobulin

PCO_2- Partial pressure of Carbon dioxide

PLT- Platelet

POPPHI- Prevention Of Post-Partum Haemorrhage Initiative

PPH- Post Partum Haemorrhage

PT- Prothrombin Time

RBC- Red Blood Cell

RR- Relative Risk

ROC- Receiver Operating Characteristics

SHS-Senior High School

TAT- Thrombin Antithrombin Complex

TFPI- Tissue Factor Pathway Inhibitor

TP- Total Protein

tPA- Tissue Plasminogen Activator

TPO- Thrombopoetin

UN- United Nations

URE- Urea

VWF- Von-Willibrand Factor

WBC-White Blood Cell

WHO- World Health Organisation

WHR- Waist to Hip ratio

α2-PI- alpha 2 Plasmin Inhibitor

Chapter 1

INTRODUCTION

1.1 GENERAL INTRODUCTION

Morbidities of pregnancy and childbirth are among the leading causes of maternal mortality in the world over. Most of these deaths occur in developing countries where living conditions are poor compared to the developed world (U.N, 2007; Ajenifuja *et al.*, 2010). Among the various causes, Postpartum Haemorrhage (PPH) especially, primary, has historically been the single most important and still is today (Rath, 2011).

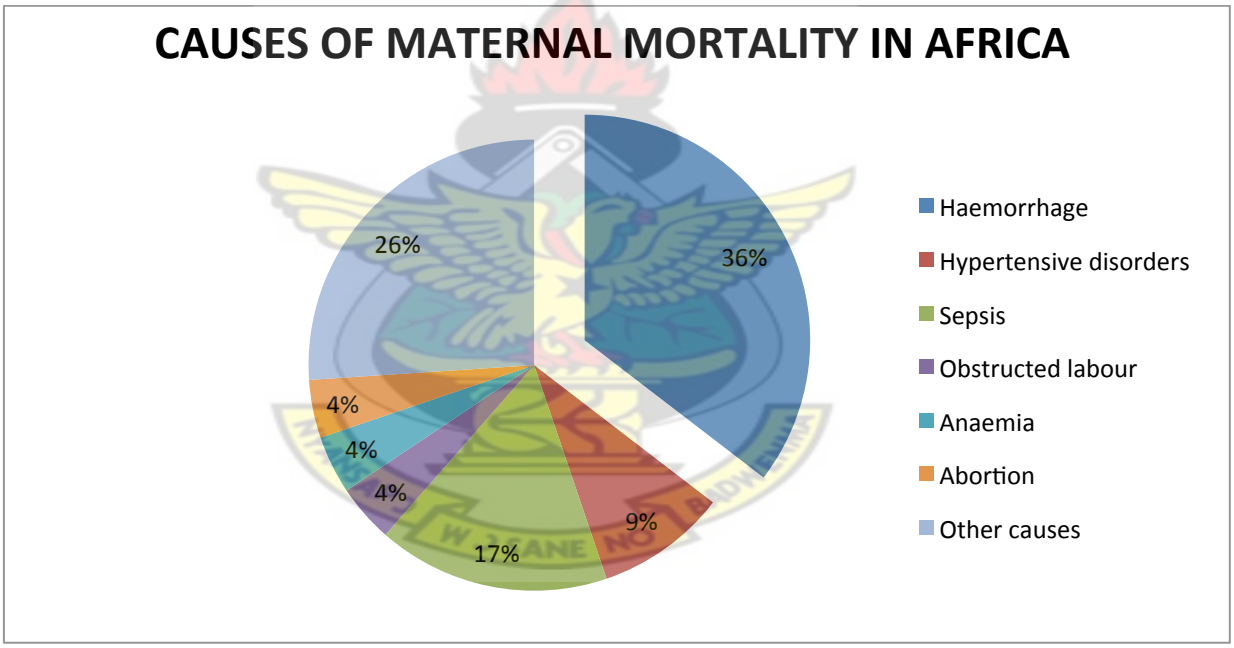


Figure 1-1 Causes of maternal mortality in Africa.
Source: (U.N, 2007)

PPH has over the years been a serious clinical problem that is of immense concern to pregnant women, health workers and all stake holders who are interested in achieving appreciable quality in reproductive health (El-Refaey and Rodeck, 2003). The condition presents with several consequences which can transform a healthy

pregnant woman in labour to a critically ill patient (NSW, 2010). It also presents with serious drills on health workers in efforts to save both the mother and baby (El-Refaey and Rodeck, 2003).

The four major causes of primary PPH are uterine atony, retained products of conception, trauma and coagulation disorders (Ramanathan and Arulkumaran, 2006). Most of these causes are observed intrapartum, at which time only interventional measures can be taken in attempts to save the mother (Ramanathan and Arulkumaran, 2006). Thus there may be other identifiable factors and conditions, which contribute to the development of primary PPH morbidity, especially those which will lead to an unhealthy uterus, ineffective haemopoesis as well as acquired bleeding disorders.

The current study therefore aimed at determining predictive factors to the occurrence of primary PPH and to evaluate visual estimation of blood loss as a diagnostic method.

1.2 STUDY HYPOTHESIS

Almost all of the causes of primary PPH are observed and met without expectation intrapartum. Visual estimation of blood loss has proven not to be a reliable method leading to a gross underestimation of primary PPH by up to 50% (NSW, 2010). The current study therefore hypothesizes that:

- Antepartum parameters could be associated with primary PPH and will have utility for screening and clinical management.
- It also hypothesises that visual estimation may not be an accurate method for the determination of blood loss and thus diagnosis of primary PPH.

1.3 JUSTIFICATION

Each year, over 500,000 women die from various complications of pregnancy and childbirth, most of which are preventable. The situation is worsened in sub-Saharan Africa, with a woman's risk of dying from maternal morbidity being 1 in 16, compared to 1 in 3,800 in the developed world (U.N, 2007). As the single most important cause of maternal deaths in Ghana and Africa, the issue of PPH has been and remains a major concern (Rath, 2011). Hence with the needed attention, the incidence of maternal deaths in Ghana will reduce drastically (Kane *et al.*, 1992; U.N, 2007).

Despite the increasing concern for primary PPH, Ghana and Africa seems to be at a set back from the 5th of the Millenium Development Goals (MDG). A number of middle-income countries have made the effort to reduce maternal mortality. These levels have been suggested as unacceptable, especially in sub-Saharan Africa and Southern Asia (U.N, 2007). In 2009, PPH was the 5th highest cause of admissions and the 4th amongst the top 10 causes of maternal deaths in Kumasi (KATH, 2009). This is an indicator that the issue is no different in Ghana, if not worse.

As reported in a study, prediction of PPH with the current antenatal screenings is poor and about 60% of cases have no identifiable risk (Maughan *et al.*, 2006; Ramanathan and Arulkumaran, 2006). Of the many demography, ante and intrapartum risk factors found to be associated with primary PPH, most of them are not predictive and are without certain basic lab investigations as a screening utility (Sheiner *et al.*, 2005). Thus taking a preventive approach can save lives (POPPHI, 2007).

It has been suggested that there is no gold standard method for blood loss estimation in most facilities, thereby posing challenges at the time of delivery (Lalonde *et al.*, 2006; Ramanathan and Arulkumaran, 2006). This may lead to an underestimation of PPH in most parts of Ghana (Duthie *et al.*, 1991).

There is generally limited data on the subject matter, especially in Ghana. The current study therefore aimed at determining and assessing various medical and haemato-biochemical parameters, their association and ability to predict the occurrence of primary PPH. It also sought to evaluate visual estimation of blood loss in the diagnosis of primary PPH.

1.4 MAIN OBJECTIVE/AIM

The current study is to investigate the ability to predict the occurrence of primary PPH by early screening with various clinical and laboratory variables.

1.4.1 Specific objectives

1. To determine the prevalence of primary PPH in Ashanti Region?
2. To determine socio-demographic, medical and past obstetric history which predispose women to primary PPH.
3. To determine a set of basal biochemical predictors of primary PPH
4. To determine a set of basal haematological predictors of primary PPH
5. To evaluate the accuracy of diagnosis of PPH with visual estimation of blood loss.

Chapter 2

LITERATURE REVIEW

2.1 POSTPARTUM HAEMORRHAGE (PPH)

In order to arrive at a more precise definition for PPH, the World Health Organisation (WHO) has made efforts by examining various studies on the subject matter. However there were challenges associated with these studies as a number of them were reported to be of poor quality (Lalonde *et al.*, 2006).

The conventional definition of PPH is a loss of 500ml or more of blood during and after vaginal delivery or a blood loss greater than 1000ml through a cesarean section. Any amount of blood loss during childbirth that compromises the haemodynamic status of the patient also constitutes PPH (Naz *et al.*, 2008; NSW, 2010).

Primary PPH is defined as blood loss within the first 24hrs after delivery (El-Refaey and Rodeck, 2003). Primary PPH can also be defined based on the site of haemorrhage. Thus a classification of placental and extra placental bleeding (El-Refaey and Rodeck, 2003).

Secondary PPH is defined as blood loss after the first 24hrs up to about 6 weeks postpartum (El-Refaey and Rodeck, 2003). As such this definition seems to reflect on time quantification rather than quantum blood loss.

Severe PPH is defined as a blood loss of 1000ml or more or any other amount of loss that causes haemodynamic compromise (NSW, 2010).

2.2 CHALLENGES ASSOCIATED WITH DEFINITION AND DIAGNOSIS

The definition of PPH, especially primary, has indeed stood the test of time. However this has not come without challenges.

It has been suggested that estimation of the exact amount of blood loss is subjective and hence there is no gold standard method for estimation in most facilities. This has posed a challenge to most facilities (Lalonde *et al.*, 2006; Ramanathan and Arulkumaran, 2006) and can lead to a gross underestimation of PPH by up to 50% (NSW, 2010). For example, it has been reported that in certain rural areas of Tanzania, the use of the "Kanga" has become the validated instrumental way of estimating blood loss (Lalonde *et al.*, 2006). The "Kanga" is a local 100cm by 155cm rectangle made of cotton fabric. When about three to four "Kangas" are observed during birth the birth attendant is entrusted to transfer the patient to a health centre.

The definition states a cut-off blood loss of 500ml or more. This means that any amount of blood loss below this volume is tolerable and does not constitute PPH. However, this is not true as certain areas where prevalence of anaemia and hypertension in pregnancy is high, women who lose as little as about 250ml of blood may constitute a serious clinical problem (El-Refaey and Rodeck, 2003; NSW, 2010). Conversely, in the developed world, women may lose about this amount and face no significant morbidity. As such the definition in this case might not be clinically relevant as well (El-Refaey and Rodeck, 2003; NSW, 2010). This is an indication that the definition does not take into account predisposing health conditions that reflect in the definition.

If the classical definition is changed, it will allow that any occurrence leading to the development of obstetric morbidity may be diagnosed based on pathophysiology, management or a combination of both (Brace and Penney, 2005).

Furthermore, if a system such as the number of units of blood transfused were to be used, it will only serve a retrospective purpose and will be of no use to a health worker who wants to treat an urgent condition like primary PPH (Brace and Penney, 2005).

It has therefore been suggested that most health workers take into account any amount of blood loss that causes signs of haemodynamic compromise rather than blood volumes (Lalonde *et al.*, 2006). Suggestions that emergency measures should be taken in cases where there is a perceived blood loss of more than one third the estimated blood volume (blood volume [ml] =weight [kg] x80), change in vital signs or loss of 1000ml or more will also be expedient (Ramanathan and Arulkumaran, 2006).

2.3 DETERMINING BLOOD LOSS IN PRIMARY PPH: VISUAL ESTIMATION VERSUS CALIBRATED MEASUREMENT

Ability to determine accurately the blood loss during childbirth is of extreme importance in the diagnosis and management of PPH. According to reports this has led to wide variations in the incidence of PPH reported in various studies (Lalonde *et al.*, 2006).

A method proposed for directly measuring blood loss objectively without interfering with routine care has been suggested (Gulmezoglu and Hofmeyr, 2002). In this study, the authors suggested that after the delivery of the baby, the amniotic fluid should be allowed to drain away, then the amniotic-soaked linen be covered with a dry disposable "linen saver". A low profile, wedge-shaped plastic "fracture bedpan" is then slipped under the woman's buttocks for blood collection. Blood together with clots are decanted into a measuring cylinder. Blood soaked swabs and "linen savers are weighed, their dry weights subtracted, and the final volume

added to that from the bedpan. This method they recommended for all future clinical trials (Gulmezoglu and Hofmeyr, 2002).

Strand and colleagues also suggested a method that used a combination of a plastic sheet and a bucket. This is placed below a cholera bed on which the woman rested during postpartum observation (Strand *et al.*, 2003).

In another study to determine blood loss at postpartum, a laboratory based method was established which included photometric techniques (Chua *et al.*, 1998). Visual estimation of blood loss has historically not been reliable compared to direct measurement. A study compared visual estimation and measured blood loss using the alkaline-haematin method during normal delivery in 37 primigravid and 25 multigravid women. The study proved that for both groups the estimated blood loss (261ml and 220ml, respectively) was significantly lower than the mean measured blood loss (401ml and 319m, respectively) (Duthie *et al.*, 1991). This study confirms suggestions that doctors and midwifes underestimate blood loss and thus PPH incidence by up to 50% (NSW, 2010).

2.4 SCALE OF THE PROBLEM

2.4.1 PPH in the world

Each year, over 500,000 women die from various complications of pregnancy and childbirth, most of which are preventable (U.N, 2007). Maternal mortality continues to be of increasing concern worldwide, the most important cause, primary PPH (Rath, 2011). The WHO estimates that PPH complicates 10.5% of all live births in the world, with an estimated 13,795,000 women experiencing this complication in the year 2000 (Anonymous, 2004). 60% of all maternal deaths occur at postpartum (Lalonde *et al.*, 2006) and in many countries haemorrhage has accounted for more than half of maternal deaths as opposed to the quarter usually

cited worldwide. An estimated 14 million women suffer from PPH every year. Among them 140,000 die whilst 1.6 million survive within a long term from anaemia (Dongol *et al.*, 2010). Even in developed countries such as the United Kingdom, United States and France, severe PPH remains amongst the first two causes of maternal deaths. Worldwide, PPH accounts for about one-fourth of 500,000 women who die of pregnancy related morbidities (Karpati *et al.*, 2004).

There are different findings on the incidence of PPH. This is due to the numerous challenges associated with the estimation of blood loss and thus diagnosis (Willis and Livingstone, 1995; Ekeroma *et al.*, 1997). As such incidence has been quoted as between 5-12% of vaginal deliveries (Willis and Livingstone, 1995; Ekeroma *et al.*, 1997). However some studies have reported lower incidences of 1.68% (Ajenifuja *et al.*, 2010) with others as high as 18% of total births (Dongol *et al.*, 2010). In a systematic epidemiological review of PPH, a worldwide incidence of 6% was reported (Carroli *et al.*, 2008).

2.4.2 PPH in Africa

Most reported maternal deaths occur in Africa with PPH accounting for about 30% of these deaths (Khan *et al.*, 2006). Almost all the maternal deaths reported in 2000 were equally distributed between Asia (253,000) and Africa (251,000), but the risk tends to be higher in Africa due to its smaller population (Lalonde *et al.*, 2006).

A study conducted in West Africa between 1994 and 1996, revealed a total of 1307 maternal morbidity cases. Obstetric haemorrhage represented the largest among the group with a total of 601 cases, of which PPH represented 342 of these cases (Prual *et al.*, 2000).

In Africa, similar or perhaps more challenges present with the estimation of blood loss and diagnosis of PPH (Willis and Livingstone, 1995; Ekeroma *et al.*, 1997). This leads to wide variations of prevalence across the continent. However in a reliable

systematic review of about 19 studies that accurately measured the blood loss, prevalence was found to be 10.5% compared to 7.23% in 22 others that estimated blood loss by visual examination (Carroli *et al.*, 2008). West Africa has the lowest prevalence of 8.6% with 18.7% and 14.2% in Middle and Eastern Africa respectively (Carroli *et al.*, 2008).

2.4.3 PPH in Ghana

There has been a reported increase in maternal mortality in Ghana (MOH, 2002) with about 34% of these deaths due to PPH (GSS, 2009). As shown in the table below Ashanti Region has always recorded the highest of maternal mortality rates, contributing significantly to national figures.

Table 2.1 Prevalence of PPH in Ghana over a five-year period.

REGION	1996	1997	1998	1999	2000
Upper East	52	42	45	43	56
Upper West	13	33	14	22	30
Northern	38	39	61	73	60
Brong-Ahafo	70	89	80	91	62
Ashanti	141	128	140	134	177
Eastern	85	101	78	121	108
Central	57	93	117	106	108
Western	44	53	78	98	104
Volta	48	60	70	97	88
Greater Accra	37	49	93	28	63
Total	585	687	777	813	851

Source: (MOH, 2002)

The trend does not seem to have changed significantly in recent times. It is estimated that about 957 women die annually in Ghana through maternal morbidities (GNA, 2011) and Ashanti Region recorded the highest maternal mortality with 222 deaths in 2008 followed by the Greater Accra and Western Regions with 167 and 101 deaths respectively (GNA, 2011). With PPH being the single most important cause of maternal mortality, it is reflected as a matter of urgent concern.

In 2009 PPH was the 5th highest cause of admissions and the 4th amongst the top 10 causes of maternal deaths at the Komfo Anokye Teaching Hospital (KATH) in Kumasi (KATH, 2009). There is however limited data on the prevalence of PPH in Ghana and Ashanti Region.

2.5 THE FEMALE REPRODUCTIVE SYSTEM

The internal genitalia of the female include the uterine tubes, uterus, and vagina. These constitute a duct system from the vicinity of the ovary to the outside of the body. The external genitalia include the clitoris, labia minora, and labia majora. They occupy the perineum, which is defined by the same skeletal landmarks as in the male. Beneath the skin of the perineum are several accessory glands that provide most of the lubrication for intercourse (Saladin, 2003).

2.5.1 The Uterine tubes

The uterine tube, also known as the oviduct or fallopian tube is a canal about 10cm long from the ovary to the uterus. At the distal (ovarian) end, it flares into a trumpet-shaped funnel with feathery projections called fimbriae; the middle part of the tube, the ampulla; and near the uterus forms a narrower isthmus. The wall of the uterine tube has significant smooth muscle. Its mucosa is extremely folded

and convoluted and has ciliated epithelium cells and a smaller number of secretory cells. The cilia beat toward the uterus, and with the help of muscular contractions of the tube, convey the egg in that direction (Saladin, 2003).

2.5.2 The Uterus

The uterus (womb) is a thick muscular chamber that opens into the roof of the vagina and usually tilts forward over the urinary bladder. It harbors the foetus, provides a source of nutrition, and expels the foetus at the end of its development. It is to a certain degree pear-shaped, with a broad superior curvature called the fundus, a mid-portion called the body (corpus), and a cylindrical inferior end called the cervix. The uterus measures about 7cm from cervix to fundus, 4cm wide at its broadest point, and 2.5cm thick, but it is fairly larger in women who have been pregnant. The lumen of the uterus is roughly triangular, with its two upper corners opening into the uterine tubes. It communicates with the vagina by way of a narrow passage through the cervix called the cervical canal. The superior opening of this canal into the body of the uterus is the internal os (mouth) and its opening into the vagina is the external os. The canal contains cervical glands that secrete mucus, thought to prevent the spread of microorganisms from the vagina into the uterus. Near the time of ovulation, the mucus becomes thinner than usual and allows easier passage for sperm (Saladin, 2003).

2.5.3 Uterine wall

The uterine wall consists of an external serosa called the parametrium, a middle muscular layer called the myometrium, and an inner mucosa called the endometrium. The myometrium constitutes most of the wall; it is about 1.25cm thick in the non-pregnant uterus. It is composed of bundles of smooth muscle running in all directions, but it is less muscular and more fibrous near the cervix;

the cervix itself is almost entirely collagenous. The smooth muscle cells of the myometrium are about 40 μm long immediately after menstruation, but they are twice this long at the middle of the menstrual cycle and 10 times as long in pregnancy. The function of the myometrium is to produce the labour contractions that help to expel the foetus. The endometrium is the mucosa. It has a simple columnar epithelium, compound tubular glands, and a stroma populated by leukocytes, macrophages, and other cells. The superficial half to two-thirds of it, called the stratum functionalis, is shed in each menstrual period. The deeper layer, called the stratum basalis, stays behind and regenerates a new functionalis in the next cycle. When pregnancy occurs, the endometrium is the site of attachment of the embryo and forms the maternal part of the placenta from which the foetus is nourished (Saladin, 2003).

2.5.4 Blood supply

The uterine blood supply is particularly important to the menstrual cycle and pregnancy. A uterine artery arises from each internal iliac artery and travels through the broad ligament to the uterus. It gives off several branches that penetrate into the myometrium and lead to arcuate arteries. Each arcuate artery travels in a circle around the uterus and anastomoses with the arcuate artery on the other side. Along its course, it gives rise to smaller arteries that penetrate the rest of the way through the myometrium, into the endometrium, and produce the spiral arteries. The spiral arteries wind tortuously between the endometrial glands toward the surface of the mucosa. They rhythmically constrict and dilate, making the mucosa alternately blanch and flush with blood (Saladin, 2003).

2.5.5 Vagina

The vagina, or birth canal, is a tube about 8 to 10cm long that allows for the discharge of menstrual fluid, receipt of the penis and semen, and birth of a baby. The vaginal wall is thin but very distensible. It consists of an outer adventitia, a middle muscularis, and an inner mucosa. The vagina tilts dorsally between the urethra and rectum; the urethra is embedded in its anterior wall. The vagina has no glands, but it is lubricated by the transudation ("vaginal sweating") of serous fluid through its walls and by mucus from the cervical glands above it. The vagina extends slightly beyond the cervix and forms blind-ended spaces called fornices. At its lower end, the vaginal mucosa folds inward and forms a membrane, the hymen, which stretches across the orifice. The hymen has one or more openings to allow menstrual fluid to pass through, but it usually must be ruptured to allow for intercourse. The lower end of the vagina also has transverse friction ridges, or vaginal rugae, which stimulate the penis and helps induce ejaculation. The vaginal epithelium is simple cuboidal in child- hood, but the oestrogens of puberty stimulate it to transform into a stratified squamous epithelium. The epithelial cells are rich in glycogen. Bacteria (*Lactobacilli*) ferment this to lactic acid, which produces a low vaginal pH (about 3.5–4.0) that inhibits the growth of pathogens. However, this acidity is neutralized by the semen so it does not harm the sperm (Saladin, 2003).

2.5.6 Vulva (Pudendum)

The external genitalia of the female are collectively called the vulva (pudendum); this includes the mons pubis, labia majora and minora, clitoris, vaginal orifice, and accessory glands and erectile tissues. It occupies most of the perineum. The mons pubis consists mainly of a mound of adipose tissue overlying the pubic symphysis. The labia majora are a pair of thick folds of skin and adipose tissue inferior to the

mons; the slit between them is the pudendal cleft. Medial to the labia majora are the much thinner, entirely hairless labia minora. The area enclosed by them, called the vestibule, contains the urinary and vaginal orifices. At the anterior margin of the vestibule, the labia minora meet and form a hood-like prepuce over the clitoris. The clitoris is structured much like a miniature penis but has no urinary role. Its function is entirely sensory, serving as the primary center of erotic stimulation. Like the penis, the internal pudendal arteries, also called the clitoral arteries in the female, supply the clitoris. Just deep to the labia majora, pair of subcutaneous erectile tissues called the vestibular bulbs brackets the vagina like parentheses. They become congested with blood during sexual excitement and cause the vagina to tighten somewhat around the penis, enhancing sexual stimulation. On each side of the vagina is a pea-sized greater vestibular gland with a short duct opening into the vestibule or lower vagina. They keep the vulva moist, and during sexual excitement they provide most of the lubrication for intercourse. The vestibule is also lubricated by a number of lesser vestibular glands. A pair of mucous paraurethral glands, homologous to the male prostate, opens into the vestibule near the external urethral orifice (Saladin, 2003).

2.6 CHANGES IN PREGNANCY

2.6.1 Digestive system, nutrition, and metabolism

For many women, one of the first signs of pregnancy is morning sickness—nausea, especially after rising from bed, in the first few months of gestation. The cause of morning sickness is however unknown. One hypothesis is that it stems from the reduced intestinal motility caused by the steroids of pregnancy (cortisol and aldosterone). Constipation and heartburn are common in pregnancy. The former is another result of reduced intestinal motility whiles the latter is due to the enlarging

uterus pressing upward on the stomach, causing the reflux of gastric contents into the esophagus. The basal metabolic rate rises about 15% in the second half of gestation (Saladin, 2003).

During the last trimester, the foetus needs more nutrients than the mother's digestive tract can absorb. In preparation for this, the placenta stores nutrients early in gestation with demands especially high for protein, iron, Ca, and phosphates. A pregnant woman needs an extra 600 mg of iron for her own haemopoesis and 375 mg for the foetus. She is likely to become anaemic if she does not ingest enough iron during late pregnancy. Supplemental vitamin K is often given late in pregnancy to promote prothrombin synthesis in the foetus. This reduces the risk of neonatal hemorrhage, especially in the brain, caused by the stresses of birth. Supplemental folic acid reduces the risk of neurological disorders in the foetus, such as spina bifida and anencephaly (failure of the cerebrum, cerebellum, and calvaria to develop). A vitamin D supplement helps to ensure adequate Ca absorption to meet fetal demands (Saladin, 2003).

2.6.2 Circulatory system

By full term, the placenta requires about 625ml of blood per minute from the mother. The mother's blood volume rises by about 30% during pregnancy because of fluid retention and haemopoesis; she eventually has about 1 to 2 L of extra blood. Cardiac output rises to about 30% to 40% above normal by 27 weeks, but for unknown reasons, it falls to almost normal in the last 8 weeks. As the pregnant uterus puts pressure on the large pelvic blood vessels, it interferes with venous return from the legs and pelvic region. This can result in hemorrhoids and varicose veins (Saladin, 2003).

2.6.3 Respiratory system

Minute ventilation increases about 50% during pregnancy for two reasons. First is that oxygen demands are about 20% higher by late pregnancy in order to supply the foetus and support the woman's increased metabolic rate. Secondly, progesterone increases the sensitivity of her respiratory chemoreceptors to carbon dioxide, and ventilation is adjusted to keep her arterial PCO_2 lower than normal. While there is a demand for increased ventilation, the expanding uterus pushes the abdominal viscera up against the diaphragm and interferes with breathing. Consequently, the respiratory rate increases to compensate for the lack of depth. Pressure on the diaphragm may be great enough to cause breathing difficulty (dyspnea) by late pregnancy. In the last month, however, the pelvis usually expands enough for the foetus to drop lower in the abdominopelvic cavity, taking some pressure off the diaphragm and allowing the woman to breathe more easily (Saladin, 2003).

2.6.4 Urinary system

Aldosterone and cortisol rise in pregnancy promote water and salt retention by the kidneys. Nevertheless, the glomerular filtration rate increases by 50% and urine out- put is slightly elevated. This enables a woman to dispose of metabolic wastes from both the foetus and her. As the pregnant uterus compresses the bladder and reduces its capacity, urination becomes more frequent and some women experience uncontrollable leakage of urine, or incontinence (Saladin, 2003).

2.6.5 Integumentary system

The skin must grow to accommodate expansion of the abdomen and breasts and the added fat deposition in the hips and thighs. Stretching of the dermis often tears the connective tissue and causes striae, or stretch marks. These appear reddish at first but fade after pregnancy. Melanocyte activity increases in some areas and darkens the linea alba and areolae. The former often becomes a dark line, the linea nigra (black line), from the umbilical to the pubic region. Some women also acquire a temporary blotchy darkening of the skin over the nose and cheeks called the "mask of pregnancy," or chloasma (to be green), which usually disappears when the pregnancy is over (Saladin, 2003).

2.6.6 Coagulation and fibrinolysis

A hypercoagulable state results in the second and especially third trimesters due to an increased synthesis and activity of several coagulation factors. The amounts of fibrinogen, coagulation factors (F) VII, VIII, IX, X, XII, and Von-Willibrand Factor (VWF) increases considerably. This leads to a shortened Prothrombin Time (PT) and activated Partial Thromboplastin Time (APTT). However, prothrombin (FII) and FV levels remain unchanged, while FXI and FXIII are slightly reduced. PLT counts have been observed to decrease during pregnancy, whereas others have observed no change. A condition known as gestational thrombocytopenia produces PLT counts between 80 and 150 × 10^9/L. The aetiology of this condition is unknown but has been attributed to the dilutional effect of pregnancy and/or a consumptive effect in the utero-placental unit, especially in the third trimester (Ahonen *et al.*, 2010).

2.7 CHILDBIRTH

2.7.1 Uterine contractility

Weaker contractions, the "Braxton Hicks contractions" of the uterus are exhibited over the course of gestation. These have the potential to become stronger in late pregnancy and can send women rushing to the hospital with "false labour." At term, however, these contractions transform suddenly into the more powerful labour contractions. Progesterone and oestrogen levels increase over the course of gestation but the former may level or decline after six months while the latter continues to rise. Progesterone is a contraction antagonist whiles oestrogen acts as an agonist. Also, as the pregnancy nears full term, the posterior pituitary releases more Oxytocin (OT) and the uterus produces more OT receptors. OT promotes labour in two ways: (i) it directly stimulates muscle of the myometrium, and (ii) it stimulates the fetal membranes to secrete prostaglandins, which acts in synergy with OT in producing labour contractions. Labour is prolonged if OT or prostaglandins are lacking, and it may be induced or accelerated by giving a vaginal prostaglandin suppository or an intravenous OT "drip." Foetal cortisol secretion rises in late pregnancy and may enhance oestrogen secretion by the placenta. The foetal pituitary gland also produces OT, which does not enter the maternal circulation but may stimulate the fetal membranes to secrete prostaglandins.

Uterine stretching is also thought to play a role in initiating labour. Stretching any smooth muscle increases its contractility, and movements of the foetus produce the sort of intermittent stretch that is especially stimulatory to the myometrium (Saladin, 2003).

2.7.2 Labour contractions

Labour contractions begin about 30 minutes apart. As labour progresses, they become more intense and eventually occur every 1 to 3 minutes. Each contraction reduces maternal blood flow to the placenta; hence the uterus relaxes periodically to restore flow and oxygen delivery to the foetus. Contractions are strongest in the fundus and body of the uterus and weaker near the cervix, thus pushing the foetus downward. According to the positive feedback theory of labour, stretching of the cervix induces labour contractions. This triggers a reflex contraction of the uterine body that pushes the foetus downward and stretches the cervix still more. Thus there is a self-amplifying cycle of stretch and contraction. In addition, cervical stretching induces a neuroendocrine reflex through the spinal cord, hypothalamus, and posterior pituitary. This causes the posterior pituitary to release OT, which is carried in the blood and stimulates the uterine muscle both directly and through the action of prostaglandins. This is also a positive feedback cycle: cervical stretching → OT secretion → uterine contraction → cervical stretching. As labour progresses, a woman feels a growing urge to "bear down." A reflex arc extends from the uterus to the spinal cord and back to the skeletal muscles of the abdomen. Contraction of these muscles (partly reflexive and partly voluntary) aids in expelling the foetus (Saladin, 2003).

2.7.3 Stages of labour

Labour occurs in three (3) main stages. Other sources however include an additional fourth stage (POPPHI, 2007). The duration of each stage tends to be longer in a primipara than in a multipara.

2.7.3.1 First stage (Dilation)

This is the longest stage, lasting 8 to 24 hours in a primipara but as little as a few minutes in a multipara. It is marked by the dilation (widening) of the cervical canal and effacement (thinning) of the cervix. The cervix reaches a maximum diameter of about 10cm (the diameter of the baby's head). During dilation, the foetal membranes usually rupture and the amniotic fluid is discharged (Saladin, 2003). There is however limited data on the consequences of a prolonged first stage on primary PPH (Magann *et al.*, 2005).

2.7.3.2 Second stage (Expulsion)

This stage typically lasts about 30 to 60 minutes in a primipara and as little as 1 minute in a multipara. It begins when the baby's head enters the vagina and lasts until the baby is entirely expelled. The baby is said to be crowning when the top of its head is visible, stretching the vulva. Delivery of the head is the most difficult part, with the rest of the body following much more easily. An episiotomy may be performed during this stage. (Saladin, 2003). There are studies that have established relationship between a prolonged second stage and primary PPH. A recent retrospective cohort study of 15,759 nulliparous term, cephalic singleton births in San Francisco divided the second stage of labour into 1hour intervals. The frequency of PPH increased from 7.1% when the second stage lasted 0–1hour to 30.9% when it lasted >4hours (Cheng *et al.*, 2004).

2.7.3.3 Third stage (Placental)

The uterus continues to contract after expulsion of the baby. The placenta, however, is a non-muscular organ that cannot contract, so it buckles away from the uterine wall. About 350ml of blood is typically lost at this stage, but contractions of the myometrium compress the blood vessels and prevent more extensive bleeding. The placenta, amnion, and other foetal membranes are expelled by uterine

contractions, which may be aided by a gentle pull on the umbilical cord (Saladin, 2003). It is at this stage that active management of labour is mostly employed. Evidence however suggests that despite this, there is an increased risk of primary PPH whenever the third stage is prolonged. A 12,979 study of vaginal deliveries was examined and found that the median duration of the third stage was 6 minutes. The incidence of PPH and blood transfusion remained constant until the third stage reached 30 minutes (3.3% of deliveries). It however increased thereafter, and reached a plateau at 75 minutes (Combs and Laros, 1991). Another study found that at all gestational ages, the frequency of PPH increased with prolongation of the third stage and reaching a plateau at 40 minutes (Dombrowski *et al.*, 1995).

Anatomy and Physiology of the Third Stage of Labour

After the baby is born, the muscles of the uterus contract rapidly. The amount of blood lost depends on how quickly this happens, since the uterus can contract more effectively after the placenta is expelled. In cases when the uterus does not contract properly (as in uterine atony), the blood vessels at the placental site stay open and haemorrhage results. Estimated blood flow to the uterus is about 500 to 800mL/minute at term, most of which passes through the placenta. The muscle fibres of the uterus are in a crosshatch (criss-cross) pattern surrounding maternal blood vessels. After the birth of the baby, these muscle fibres begin to contract and retract, ultimately reducing the uterine size. OT, a hormone secreted by the posterior pituitary gland, stimulates uterine contractions (POPPHI, 2007).

The placental separation takes place by contraction and retraction of the uterine muscles, reducing the size of the placental area of attachment. As the placental area becomes smaller, the placenta begins to separate from the uterine wall. Unlike the uterus, the placenta is not elastic and cannot contract and retract (a property

enabling the detachment process). At the area where the placenta separates from the uterus, a clot known as a retroplacental clot collects between the uterine wall and the placenta and further promotes separation. Additional uterine contractions complete the separation of the placenta from the uterine wall (POPPHI, 2007)

2.7.3.4 Fourth stage ("immediate postpartum")

The fourth stage of labour begins with delivery of the placenta and goes from one to six hours after delivery of the placenta, or until the uterus remains firm on its own. In this stabilization phase, the uterus makes its initial readjustment to the non-pregnant state. The primary goal is to prevent haemorrhage from uterine atony and the cervical or vaginal lacerations (POPPHI, 2007).

2.8 CAUSES OF PPH

Primary PPH can occur from four main causes usually known as the"4Ts"mnemonic. These can occur individually or in combination to cause obstetric haemorrhage. They are: Tone (poor uterine contraction after delivery), Trauma (to the genital tract), Tissue (retained products of conception or blood clots) and Thrombin (coagulation abnormalities) (Ramanathan and Arulkumaran, 2006).

Table 2.2 Causes of PPH

CAUSE	AETIOLOGY
Tone (70%)	Atonic uterus, Over distended uterus, Uterine muscle exhaustion, Intra-amniotic infection, Drug-induced uterine hypotonia, Functional or anatomic distortion of the uterus
Trauma (20%)	Episiotomy or lacerations, Extensions / lacerations at caesarean section, Uterine rupture, Uterine inversion
Tissue (10%)	Retained products, Abnormal placenta, Retained cotyledon or succenturiate lobe
Thrombin (1%)	Retained blood clots, Coagulation disorders acquired during pregnancy, Idiopathic Thrombocytopenic Purpura (ITP), Von- Willebrand's disease, Haemophilia, Thrombocytopenia with pre-eclampsia, Disseminated Intravascular Coagulation (DIC), Pre-eclampsia, Retained dead foetus, Severe infection, Placental abruption, Amniotic fluid embolism

SOURCE: (NSW, 2010)

2.8.1 Tone

The most common cause of PPH is uterine atony (failure of the uterus to contract). It is responsible for about 75% - 90% of PPH (NSW, 2010). This occurs when the relaxed myometrium fails to constrict the blood vessels that supply it, thereby allowing haemorrhage (POPPHI, 2007). In this case, death from haemorrhage is highly possible as about one-fifth of the maternal cardiac output enters the utero-placental circulation at term. The usual predisposing factors are prolonged or precipitate labour, overdistention of the uterus, antepartum haemorrhage, deep anaesthesia, and mismanagement of the third stage (Melody, 1951). Studies to suggest evidence of certain risk factors for uterine atony after vaginal delivery are

limited. A study found multiple gestation, Hispanic race, induced or augmented labour for >18hr, infant birth weight 4.5kg and clinically diagnosed chorio-amnionitis as risk factors for uterine atony (Rouse *et al.*, 2005).

2.8.2 Trauma

Injury to the uterovaginal tract is also a major cause of PPH and accounts for about 20% of cases (Anderson *et al.*, 2000). The anatomical lesions are cervical and vaginal lacerations, including rupture of the vagina, paravaginal hematomas, and rupture of the uterus. The possibility of these complications should be thought of after precipitate delivery, after difficult obstetrical manoeuvres, and with the parturition of elderly primiparae (Melody, 1951). A study has shown that the odds of PPH in genital trauma is 1.7 with a diagnostic criteria of >1000ml blood loss (Magann *et al.*, 2005).

2.8.3 Tissue

Retained placenta accounts for about 10% of PPH causes (Anderson *et al.*, 2000). Effective uterine contraction to aid haemostasis requires complete expulsion of the placenta (Melody, 1951). Many studies have proven that retained products of conception are associated with increased blood loss and the need for blood transfusion. In one such study, retained placenta was found to be associated with an OR of 7.83 (95%CI 3.78–16.22) and 11.73 (95% CI 5.67–24.1) for PPH of ≥ 500ml and PPH of ≥ 1000ml, respectively (Bais *et al.*, 2004).

2.8.4 Thrombin

Disorders of the clotting cascade and platelet dysfunction are the cause of PPH in 1% of cases (Anderson *et al.*, 2000). Placental abruption, pre eclampsia, septicaemia and intrauterine sepsis, retained dead foetus, amniotic fluid embolus, incompatible blood transfusion, abortion with hypertonic saline and existing coagulation

abnormalities have been established as known associations with coagulation disorders in pregnancy (Griffiths and Howell, 2003).

2.9 ANTENATAL RISK FACTORS FOR PPH

***Age*:** Increased maternal age is an independent risk factor for PPH. In a study conducted In Zimbabwe, it was reported that advanced maternal age (≥ 35 years) was associated with an adjusted RR of 3.0 (95% CI 1.3–7.3) for PPH (Tsu, 1993) . Another found that the risk of PPH in women >35 years was two-fold higher compared to women <25 years (Ijaiya *et al.*, 2003).

***Ethnicity*:** Ethnicity can be associated with the risk for PPH. Asian race has been established as a risk factor (OR 1.8, 95% CI 1.4–2.2) (Magann *et al.*, 2005).

***Body Mass Index (BMI)*:** Women who are obese have higher rates of intrapartum and postpartum complications. A population-based observational study of 60167 deliveries in South Glamorgan, UK, found that women with a BMI > 30 had an OR of 1.5 (95% CI 1.2–1.8) compared to women with a BMI of 20–30 (Usha *et al.*, 2005).

***Parity*:** Over the years, grand multiparity has been thought of as a risk factor for PPH. However, some studies have revealed contrary. Two studies found no relation between grand multiparity and significant obstetric haemorrhage (Stones *et al.*, 1993; Selo-Ojeme and Okonofua, 1997). Another study has reported an association with low parity (0–1 previous birth) with adjusted RR of 1.5 and 1.7 with and without intrapartum factors respectively (Tsu, 1993).

***Prolonged pregnancy*:** A large cohort study has suggested an association of prolonged pregnancy with PPH (Olesen *et al.*, 2003).

***Foetal macrosomia*:** It has been suggested that a birth weight >4kg is better at predicting maternal morbidity. PPH is thus increased in women with foetal macrosomia (Jolly *et al.*, 2003).

***Multiple pregnancies*:** Few studies have suggested that twins and other high order pregnancies are associated with obstetric haemorrhage. Multiple pregnancies are associated with an increased risk for PPH (RR 1.88, 95% CI 1.81–1.95) (Bais *et al.*, 2004; Walker *et al.*, 2004)

***Fibroids*:** Sources have indicated that fibroids are associated with a risk for PPH. However, these have mostly been based on case reports (Akrivis *et al.*, 2003). A cohort study in Japan found a similar association in women with leiomyoma's (Ohkuchi *et al.*, 2003).

***Antepartum haemorrhage*:** This has been linked with the development of PPH. There is evidence of a RR for PPH (>1000ml) of 12.6 for proven abruption and 13.1 and 11.3 for previa with and without bleeding (Stones *et al.*, 1993).

***History of PPH*:** Women with a previous history of PPH have been demonstrated to have an increased risk for subsequent PPH episodes (Magann *et al.*, 2005).

***History of previous caesarean section*:** There is evidence that women are more likely to bleed more at vaginal delivery when they have had a previous caesarean section (Ohkuchi *et al.*, 2003).

***Other conditions*:** Several other medical conditions have also been found to increase the risk of PPH. Some of which are type II diabetes mellitus, connective tissue disorders like Marfan's and Ehlers Danlos syndrome (Rahman *et al.*, 2003; Dunne, 2005). Inherited and acquired bleeding disorders like the Haemophilia A and B and Von-Willebrand's disease are also contributing factors (Economides *et al.*, 1999).

2.10 COMPLICATIONS OF PPH

PPH comes with various complications that can transform a healthy looking mother to a very ill looking one in a few minutes. Complications include: hypovolaemic shock, Sheehan's syndrome, other organ disorders due to reduced perfusion, coagulopathy, anaemia, blood transfusion/reactions and its associated reactions, hysterectomy, lactation difficulties and ultimately, death.

Sheehan's syndrome: In PPH, massive loss of blood can lead to insufficient perfusion of organs like the pituitary gland and cause cell death. When cell death occurs in more than 10% of the gland, the patient begins to suffer symptoms of anterior pituitary insufficiency. They include lactation difficulties, weakness, lethargy, decreased sweating, hypersensitivity to cold, shrinking in size of the external genitalia, amenorrhoea or oligomenorrhoea, loss of hair and absence of menopausal symptoms.

2.11 PPH PREVENTION

It is very difficult to predict which woman will develop primary PPH, except has gone through a series of assessment of risk factors and conditions, which make her prone to this complication. When a woman develops primary PPH, positive outcomes will depend on how healthy the woman was before developing PPH (e.g. haemoglobin levels), how quick a diagnosis can be made and how quickly an effective treatment regimen can be administered after PPH begins (POPPHI, 2007).

During Antenatal Care: It has been suggested that health care professionals design screening and counselling programs, aimed at detecting and managing pregnancy-related conditions. In addition, a complication readiness program which is patient oriented should also be put in place to ensure safe delivery (POPPHI, 2007).

During labour and second stage: It has been suggested (POPPHI, 2007) that health care providers observe all necessary steps including the use of partographs, early referrals and encouragement of the woman to follow proper clinical labour guidelines.

During third stage: The recent Active Management of Third Stage of Labour (AMTSL) is often recommended over the conventional physiologic (expectant) approach to managing this stage of labour. (POPPHI, 2007). The table 2.3 describes the merits and demerits of the two modes of management of the third stage.

After delivery of the placenta: Routine inspection of the female genitalia and the general condition of the woman is advised at regular intervals, until about 6hr postpartum (POPPHI, 2007).

Table 2.3 Comparison of active and expectant management of labour.

	Physiologic (expectant) management	**Active management**
Advantages	Does not interfere with normal labour process. Does not require special drugs/supplies. May be appropriate when immediate care is needed for the baby (such as resuscitation) and no trained assistant is available. May not require a birth attendant with injection skills.	Decreases length of third stage. Decrease likelihood of prolonged third stage. Decreases average blood loss. Decreases the number of PPH cases. Decreases need for blood transfusion.
Disadvantages	Length of third stage is longer compared to AMTSL. Blood loss is greater compared to AMTSL. Increased risk of PPH	Requires uterotonic and items needed for injection/injection safety. Requires a birth attendant with experience and skills giving injections and using CCT (Controlled Cord Traction).

Source (POPPHI, 2007)

2.12 BLEEDING AND COAGULATION

The normal haemostatic response to vascular damage depends on closely linked interaction between the blood vessel wall, circulating platelets and blood coagulation factors. Therefore an efficient mechanism for stopping bleeding from various sites of vascular injury is essential for survival. The five major components involved are platelets, coagulation factors, coagulation inhibitors, fibrinolysis and blood vessels (Hoffbrand *et al.*, 2006).

2.12.1 Platelets

The bone marrow is the main site of production of platelets. Haemopoetic stem cells differentiate from megakaryoblasts to megakaryocytes, which gives rise to platelets via fragmentation. The liver and kidneys constitutively produce Thrombopoetin (TPO), the major regulator of platelet production, increasing the number and rate of maturation of megakaryocytes via c-Mpl receptors, ultimately leading to platelet production. There is evidence that platelet numbers begin to rise 6 days after start of TPO therapy and remain high for about 7 to 10 days. However platelets also have c-Mpl receptors and thus remove TPO from circulation, a self-regulatory mechanism. The normal PLT count is approximately 250 x 10^9/L (range 150-400 x 10^9 /L) with a lifespan is 7-10 days. The main function of platelets is the formation of mechanical plugs during the normal haemostatic response to vascular injury. In the absence of platelets, spontaneous leakage of blood through small vessels may occur (Hoffbrand *et al.*, 2006).

2.12.2 Coagulation

Blood coagulation involves a biological amplification system in which initiation substances sequentially activate by proteolysis, a series of circulating coagulation factor enzymes. This process leads to the generation of thrombin and ultimately fibrinogen to fibrin. Fibrin enmeshes the platelet aggregates at the sites of vascular injury and converts the unstable primary platelet plugs to firm, definitive and stable haemostatic plugs (Hoffbrand *et al.*, 2006).

The coagulation cascade

Initiation of the coagulation cascade involves two distinct pathways, the extrinsic and intrinsic. In the intrinsic pathway, tissue factor binds to factor VII or VIIa in a 1:1 complex, upon vascular injury. Limited proteolysis leads to a tissue

factor/factor VIIa complex that can activate factor X or factor IX to activated serine proteases through cleavage of an activation peptide. Once this pathway commences, the tissue factor/factor VIIa activation of factor X is rapidly shut down by an inhibitor produced by endothelial cells, Tissue Factor Pathway Inhibitor (TFPI). The newly activated factor IXa then binds to its cofactor, factor VIIIa, on a phospholipid surface to form the tenase complex that results in the activation of factor X to factor Xa. The activation of factor X to Xa starts the final, common pathway for thrombin activation. Factor Xa combines with the cofactor, factor Va, together with Ca on phospholipid surfaces to form the prothrombinase complex. This complex then effects the conversion of prothrombin to thrombin by cleavage of an activation peptide, prothrombin. The generation of a small amount of thrombin initiated by extrinsic means appears to be enough to start the coagulation mechanism and, if conditions are right, the expansion of thrombin generation through an intrinsic mechanism. The intrinsic portion of the pathway include activation of factor XI to factor XIa by thrombin, with the ultimate generation of more thrombin using factor IXa and factor VIIIa to activate factor X (Triplett, 2000; Hoffman, 2003).

INTRINSIC SYSTEM **EXTRINSIC SYSTEM**

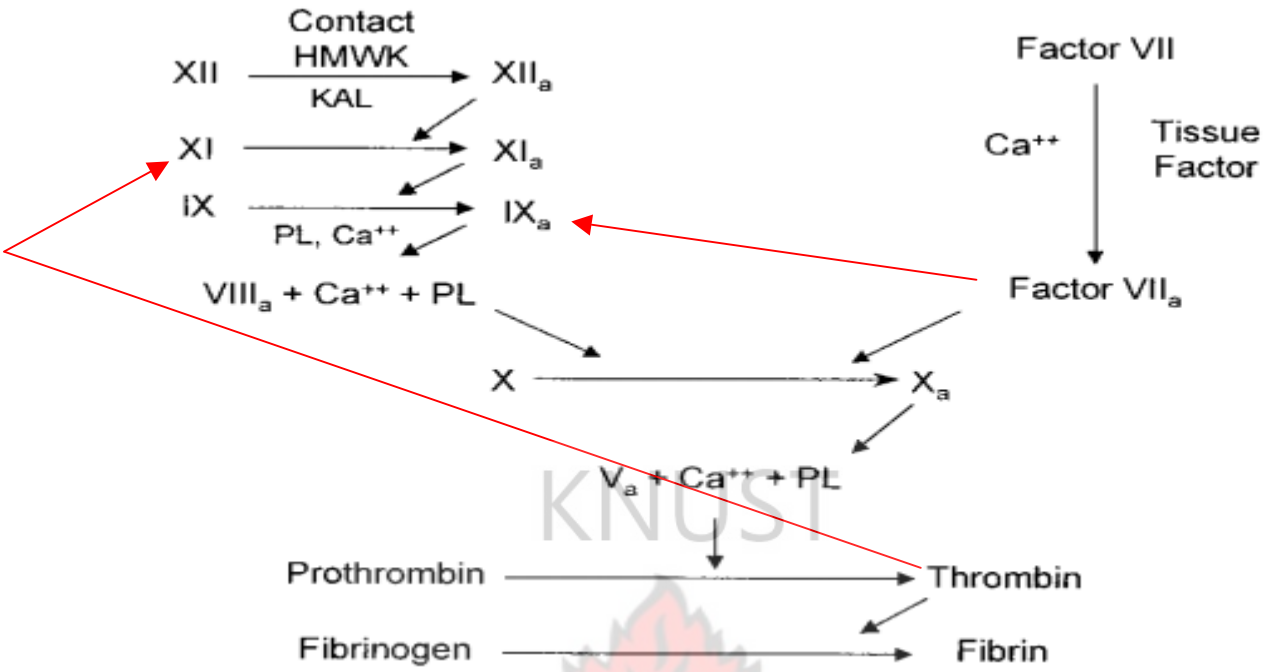


Figure 2-1 Schematic presentation of the coagulation cascade.

Source: (Triplett, 2000).

Key: HMWK-high molecular weight kininogen; Kal-kallikrein; PL-phospholipid; Ca^{++}-ionic calcium; subscript "a" denotes the activated form of the coagulation factors (e.g. factor XIIa, factor VIIa). NB: Kal and XII are relevant in in vitro testing. HMWK, V and VIII are co-factors.

Table 2.4 Families of coagulation proteins.

Vitamin K dependent	Fibrinogen	Contact
Factor II	Fibrinogen	Factor XII
Factor VII	Factor V	Factor XI
Factor IX	Factor VIII	Prekallikrein
Factor X	Factor XIII	HMWK

Source: (Triplett, 2000)

2.12.3 Tests of Haemostasis

Various investigations which can be done to assess haemostasis include; Bleeding time, Clotting time, platelet count, Fibrinogen concentration, Thrombin Time, levels of Fibrin Degradation Products such as n-dimers in serum and urine, PT and APTT, Blood film examination.

Correction studies help to distinguish factor deficiencies from inhibitors in cases of abnormality. (Collins *et al.*, 2011).

Table 2.5 Typical Results in haemostasis disorders.

	PLT count	PT	APTT	TT
Liver disease	Low	Prolonged	Prolonged	Normal
DIC	Low	Prolonged	Prolonged	Grossly prolonged
Massive transfusion	Low	Prolonged	Prolonged	Normal
Oral anticoagulants	Normal	Grossly prolonged	Prolonged	Normal
Heparin	Normal	Mildly prolonged	Prolonged	Prolonged
Circulating anticoagulants	Normal	Normal or prolonged	Prolonged	Normal

Source (Hoffbrand *et al.*, 2006)

2.13 THE LIVER AND ITS ROLE IN HAEMOASTASIS

The liver plays a vital role in haemostasis as it synthesises most of the coagulation factors, anticoagulant proteins and components of the fibrinolytic system. Additionally, its reticuloendothelial system helps to regulate coagulation and fibrinolysis by clearing these coagulation factors from the circulation. Impaired

haemostasis resulting from abnormal liver function is often due to many factors and may include impaired coagulation factor synthesis, synthesis of dysfunctional coagulation factors, increased consumption of coagulation factors, altered clearance of activated coagulation factors and quantitative and qualitative platelet disorders (DeSancho and Pastores, 2008).

Clotting factors synthesised by the liver include FII, FVII, FIX, FX, Proteins C, S and E. These factors require vitamin K as a co-factor for post-ribosomal modification to render them active. Thus are often referred to as vitamin K dependent. Notable one's also include, FV, FXIII, Fibrinogen, Antithrombin, alpha 2- plasmin Inhibitor (α2-PI), Plasminogen, VWF, Tissue Plasminogen Activator (tPA), Thrombomodulin and TFPI (DeSancho and Pastores, 2008).

2.13.1 Haemostatic abnormalities in liver disease

Abnormalities in haemostasis can occur in patients with liver diseases and the extent of abnormality is mostly dependent on the extent of liver disease (DeSancho and Pastores, 2008).

Acute liver disease

Both quantitative and qualitative abnormalities in coagulation factors are observed. Commonly, the vitamin K-dependent factors decrease first, especially factor VII and protein C, followed by factor II and X (Mammen, 1994; DeSancho and Pastores, 2008).

Fibrinogen levels are rarely decreased and may be elevated due to abnormal non-functional fibrinogen (dysfibrinogenaemia) related to defective polymerization. A decrease in fibrinogen levels may indicate the presence of DIC or progression to fulminant hepatitis with hepatic failure. In patients with acute fulminant hepatic failure, alterations are attributed to quantitative and qualitative platelet defects,

impaired synthesis and clearance of the coagulation factors and related inhibitory proteins and enhanced fibrinolysis.

In acute fulminant hepatic disease, activities of plasminogen and its inhibitor α2-PI are reduced while tPA and Plasminogen Activator Inhibitor (PAI-1) activities are normal and increased respectively. This is an indicator of a shift towards inhibition of fibrinolysis in these patients. Thrombin Antithrombin (TAT) complex levels and D-dimer, a fragment of cross-linked fibrin in plasma, are also significantly increased, indicating activation of coagulation and fibrinolysis respectively. Thus, gross abnormalities of the fibrinolytic system occur in fulminant liver failure but inhibitory activity appears to limit the incidence of bleeding due to fibrinolysis (Pernambuco *et al.*, 1993).

Factor V levels are decreased in both acute and chronic liver disease (Mammen, 1994).

Chronic liver disease

In patients with liver cirrhosis, most coagulation factors and inhibitors of the coagulation and fibrinolytic systems are markedly reduced due to impaired protein synthesis, except for factor VIII and fibrinogen levels, which may be normal or increased (DeSancho and Pastores, 2008). Increased factor VIII levels may be due to the increased hepatic biosynthesis of VWF and decreased expression of LDL receptor-related protein, both of which modulate the level of factor VIII in plasma, rather than increase factor VIII synthesis (Hollestelle *et al.*, 2004). The deficiencies in vitamin K-dependent factors in cirrhosis may occur by several mechanisms, including reduced hepatic synthesis and reduced absorption of bile salts required for absorption of vitamin K-dependent factors, which may occur in cholestatic liver disease. Other contributing factors include poor oral intake and treatment with antibiotics that destroy the intestinal bacteria that

synthesize vitamin K. As with acute liver disease, the reductions in coagulation factors parallel the degree of progression of liver disease (Kujovich, 2005; DeSancho and Pastores, 2008).

Impaired synthesis and altered clearance of the fibrinolytic factors are the causes of the complex abnormalities of the fibrinolytic system. One of the striking mechanisms is an imbalance between tPA and α2-PI resulting in free tPA (Colucci *et al.*, 2003)

The levels of TAFI are markedly reduced in cirrhotic patients and correlate with the severity of disease (Colucci *et al.*, 2003).

Cirrhotic patients also have a significant reduction of natural anticoagulants, predominantly protein C and antithrombin (Castelino and Salem, 1997). Activated protein C in combination with its cofactor protein S, downregulates thrombin generation by inhibiting the action of the cofactors factors Va and VIIIa. Downregulation by the TFPI by specifically inhibiting the complex of TF and VIIa is also another mechanism (Rosenberg and Aird, 1999).

According to some studies, the standard PT and APTT may not reflect the true coagulation status of patients with liver cirrhosis. This is due to the activation of the primary endogenous anticoagulant protein C, levels of which are considerably reduced in cirrhosis. It has been concluded that thrombin generation is normal in cirrhosis and that the reduction in procoagulant factors in these patients is compensated for by the reduction in anticoagulant factors, thus leaving the coagulation balance unaltered (Tripodi *et al.*, 2005)

2.13.2 Thrombocytopenia

Quantitative and qualitative abnormalities such as impaired platelet adhesion and aggregation may develop in patients with liver diseases (Hoffbrand *et al.*, 2006). The aetiology of thrombocytopenia in these patients is often attributed to splenic sequestration (hypersplenism). It has however been reported that aetiology may also be as a result of platelet destruction mediated by Platelet Associated Immunoglobin (PAIgG) (Sanjo *et al.*, 2003) and impaired hepatic synthesis and/or increased degradation of TPO by platelets sequestered in the congested spleen (Rios *et al.*, 2005). Ethanol is known to supress the formation and decrease the lifespan of platelets, a phenomenon commonly seen in alcohol related liver diseases (Scharf and Aul, 1988). The thrombocytopenia may result from folate deficiency, direct toxic effects of ethanol on megakaryocytopoiesis and increased platelet activation (DeSancho and Pastores, 2008). Some medication, folate and B12 deficiencies, severe infections, DIC are other common causes of thrombocytopenia (Hoffbrand *et al.*, 2006). In chronic liver diseases, increased platelet sequestration and destruction is due to hypersplenism secondary to portal hypertension (DeSancho and Pastores, 2008). Diminished protein synthesis in the liver has been reported to cause inadequate synthesis of TPO. TPO levels are significantly lower in cirrhotic patients with thrombocytopenia than in those with normal platelet and levels correlate inversely with the severity of liver disease (Ishikawa *et al.*, 2002; Panasiuk *et al.*, 2004).

2.13.3 Disseminated Intravascular Coagulation (DIC)

Low-grade DIC is commonly found in patients with End Stage Liver Disease (ESLD). It is typically characterized by thrombocytopenia, prolongation of the PT and APTT, decreased fibrinogen and elevated levels of fibrin degradation products (FDPs). The frequency and severity of DIC tends to correlate with the stage of liver

disease (DeSancho and Pastores, 2008). The aetiology of DIC in chronic liver disease is due to several factors. They include release of procoagulants from injured hepatocytes, impaired clearance of activated clotting factors, decreased synthesis of coagulation inhibitors and endotoxin entry into the portal circulation (Kujovich, 2005).

2.13.4 Laboratory findings for coagulation in liver disease

Often, the clotting tests remain normal until clotting factor levels fall to less than 30–40% of normal. In mild liver disease, the PT is prolonged, but the APTT is usually normal whiles both PT and APTT levels are prolonged as the disease progresses. In compensated cirrhosis however, the high factor VIII level may blunt the prolongation of the APTT (DeSancho and Pastores, 2008). Fibrinogen levels are either normal or increased in patients with stable chronic liver disease. In decompensated cirrhosis or DIC, there is a marked decrease in fibrinogen levels (< 100 mg/dL), resulting in marked prolongation of the PT, APTT and TT (DeSancho and Pastores, 2008).

2.14 THE KIDNEYS

The kidneys play an important role in the maintenance of normal body function. The basic function of the kidney is the formation of urine through complex filtration, reabsorption and secretion mechanisms. In addition, the kidneys excrete urea and uric acid, the end products of protein and nucleic acid metabolism. The kidneys regulate fluid, electrolyte and acid base balance of the body and create a steady environment for the metabolic processes of tissues and cells.

The kidney also produces three (3) important hormones; erythropoietin which stimulates the production of red blood cells, renin which regulates blood pressure and calcitriol which helps in regulation of plasma Ca levels.

Anaemia usually develops in various forms of kidney diseases and worsens as the disease progresses.

Renal perfusion reduces and increases the risk of the development of increased cardiac output and thus a high blood pressure.

2.14.1 Haemostatic disorders in kidney disease

Bleeding disorders are common in renal diseases, especially in chronic kidney disease. However, with dialysis most patients escape most of these manifestations (Hoffbrand *et al.*, 2006). Bleeding is seen despite normal or elevated circulating levels of coagulation factors, suggesting that platelet abnormalities are the likely cause. This is supported by the finding of a prolonged bleeding time and reduced platelet aggregation to various agonists. Severe thrombocytopenia (PLTs $< 50 \times 10^9$/L) secondary to renal failure is rare and its presence should suggest concomitant conditions such as HCV infection or vasculitis (Collins *et al.*, 2011). Failure of the kidney to produce adequate amounts of TPO for the production and maturation of platelets may also be a factor (Hoffbrand *et al.*, 2006).

Platelet dysfunction with renal failure is multifactorial and can be divided into (i) intrinsic platelet defects, (ii) abnormal interaction of platelets with the endothelium, (iii) effects of uraemic toxins, (iv) effects of anaemia on platelets and (v) dialysis-related.

The interaction between uraemic platelets and the endothelium can be markedly reduced, partly due to impaired VWF binding to platelets. Excess urea can cause an upregulation of endothelial nitric oxide through shunting of L-arginine to form guanidinosuccinic acid. This can inhibit platelet aggregation. Anaemia-related

haemostatic dysfunction is primarily a result of reduced displacement of platelets to the vessel wall by red cells. Decreased red cell number also results in reduced ADP release and decreased platelet interaction with collagen (Collins *et al.*, 2011).

2.15 ANAEMIA

The word anaemia originates from a Greek word, "anaimia" meaning lack of blood. It is defined as a reduction in the number of red blood cells or the level of haemoglobin in the blood below the acceptable levels for age and sex. It can also include a decrease in oxygen binding ability of each haemoglobin molecule as occurs in certain types of haemoglobin deficiencies. Because of the important function of Haemoglobin (HGB), anaemia usually leads to hypoxia in various organs and comes with varying degrees of consequences (Hoffbrand *et al.*, 2006).

2.15.1 Signs and symptoms

The signs and symptoms can be related to the anaemia itself, or the underlying cause. People with anaemia commonly report with non-specific symptoms of weakness, fatigue, general malaise, dyspnoea and sometimes, poor concentration. Cardiac output may increase as a result of compensation presenting with palpitations, angina (if there is a pre-existing heart disease), intermittent claudication and sometimes heart failure are symptoms patients may exhibit due to increased cardiac output (Hoffbrand *et al.*, 2006).

Signs exhibited may include pallor, koilonychia (in iron deficiency), jaundice (in haemolytic anaemia), bone deformities (in thalassemia major) or leg ulcers (in sickle cell disease). In severe anaemia, there may be signs of a hyperdynamic

circulation: bounding pulse, tachycardia, flow murmurs, and cardiac ventricular hypertrophy. There may also be signs of heart failure (Hoffbrand *et al.*, 2006).

A phenomenon known as Pica, the consumption of non-food based items such as dirt, paper, wax, grass, ice, and hair, may be a symptom in those with iron deficiency. Symptoms which are less common may include swelling of the legs or arms, blood in stool, vague bruises, vomiting, increased sweating, and chronic heartburn (Hoffbrand *et al.*, 2006).

2.15.2 Diagnosis

Diagnosis of anaemia is usually by a Complete Blood Count (CBC) and examination of a blood stained smear under a microscope (Hoffbrand *et al.*, 2006). Where the diagnosis is difficult, other tests are employed. They include, serum ferritin, vitamin B12, transferrin, iron, RBC folate, HGB electrophoresis and renal function tests are employed (Hoffbrand *et al.*, 2006).

2.15.3 Grading of anaemia

Grade 1 (Mild Anaemia): 10 g/dl - cut-off point for ages

Grade 2 (Moderate Anaemia): 7-10 g/dl

Grade 3 (Severe Anaemia): below 7 g/dl (WHO, 1989)

2.15.4 Anaemia and pregnancy

As a result of the normal physiological changes in pregnancy, plasma volume expands by 46 to 55%, while red-cell volume expands by 18 to 25%. This results in a haemodilution which is usually termed physiological anaemia in pregnancy (Hoffbrand *et al.*, 2006). Estimates show that over half the pregnant women in the world have a HGB level, which indicates anaemia, a situation which calls for concern. However, this still reaches the level of public health significance (≥ 10%). Prevalence for developing countries range from 35% to 72% for Africa, 37 to 75%

for Asia and 37 to 52% for Latin America (WHO, 1992). Maternal mortality resulting from anaemia range from 34 per 100,000 live births in countries like Nigeria to as high as 194/100,000 in Pakistan (WHO, 1992). Anaemia is estimated to be responsible for 17–46% of cases of maternal death when combined with obstetric haemorrhage (Carroli *et al.*, 2008). Complications of PPH, pre-term delivery and foetal growth restriction are more frequent in anaemic women (Fareh *et al.*, 2005). This is an indicator that anaemia in pregnancy predisposes to morbidities and must be controlled.

Chapter 3

MATERIALS AND METHODS

3.1 STUDY DESIGN

The study was carried out from April to October 2012. It was a nested case-control design with simple random sampling of women admitted to deliver at the labour ward of the KATH, Kumasi.

345 women at term and in first stage of labour were recruited as a start cohort from the labour ward of the Obstetrics and Gynaecology (O & G) department of the KATH. From the total population, 271 women went through normal vaginal delivery and 74 women underwent caesarean section. Of the 271 women, 55 developed primary PPH and were categorised as cases whiles the remaining 216 who delivered without such morbidity were categorised as controls. All 74 women who delivered via caesarean section were excluded.

Sample size justification

The following formula was used:

$$N = \frac{t^2 \times P(1 - P)}{m^2} \qquad m^2$$

Where;

N: sample size, t: confidence interval of 95% (standard value of 1.96), **P**: prevalence rate (8.6%) (Carroli *et al.*, 2008), **m**: margin of error (standard value of 0.05).

Hence **N= 121.**

A minimum of 121 partcicpants was required. Therefore, a higher sample number of 345 was used.

3.2 RECRUITMENT OF PARTICIPANTS

To qualify for recruitment, the women must be reporting on admission to the KATH O & G for delivery. Delivery must be vaginal and the patient must have no chronic illnesses such as Diabetes Mellitus, HIV and Tuberculosis. Screening tests for HIV and Hepatitis B surface antigen were done on patient samples for confirmation. Other relevant information for recruitment was obtained from patient folders. Diagnosis of primary PPH was based on a strict clinical criterion, which was defined in the current study.

All of the respondents are indigenes of Ghana and participation in the study was entirely voluntary.

The objective of the study was explained to each participant and informed consent was obtained. The study was approved by the Committee on Human Research Publication and Ethics (CHRPE) of the Kwame Nkrumah University of Science and Technology (KNUST)/ School of Medical Sciences (SMS) and the Research and Development unit of the KATH.

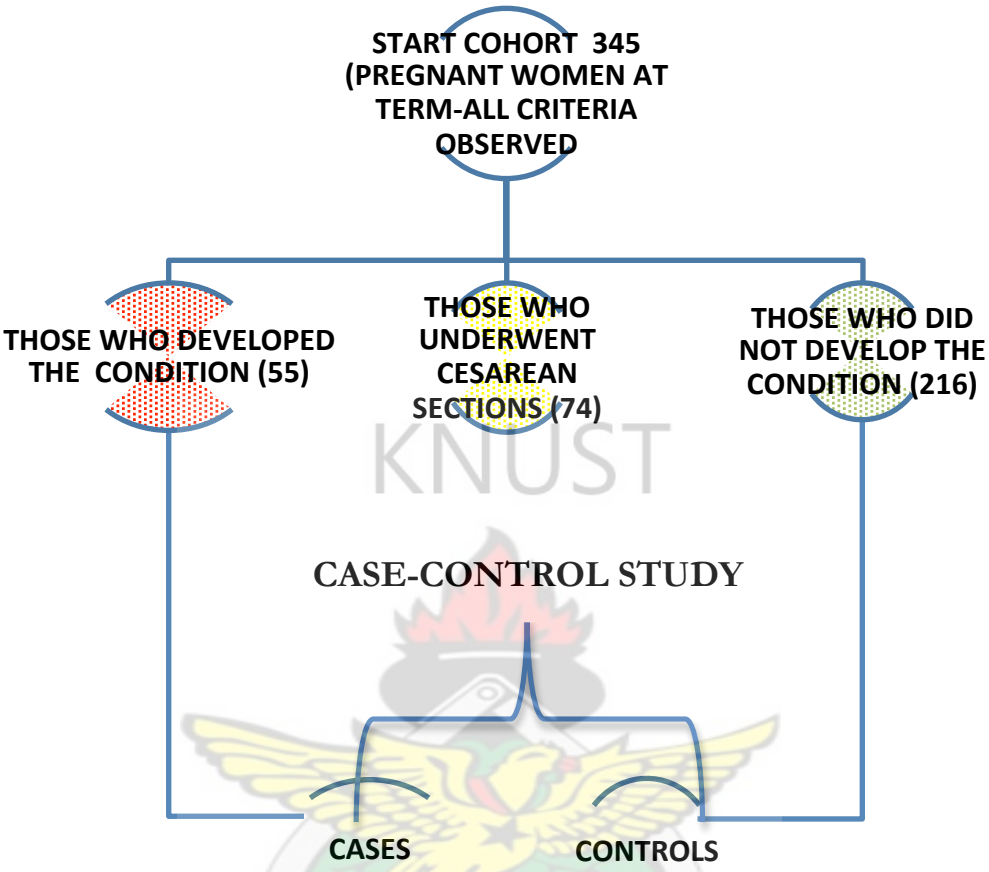


Figure 3-1 Schematic representation of study design and recruitment process

3.3 ADMINISTRATION OF QUESTIONNAIRES

A questionnaire was prepared and administered to study participants upon recruitment. It was prepared in the English language but translated into the local Ghanaian dialects as appropriate during administration. The questionnaire sought to gather information on demography, anthropometry, clinical and obstetric history. The questionnaire was pre- tested before commencement of the study.

3.4 MEASUREMENT OF ANTHROPOMETRIC VARIABLES

Anthropometric measurements included height (to the nearest 0.5cm) and weight (to the nearest 0.1kg) without shoes and in light clothing. Subjects were weighed on a bathroom scale (Zhongshan Camry Electronic Co. Ltd, Guangdong, China) and their height measured with a wall-mounted ruler. Body mass index (BMI) was calculated by dividing the weight (kg) by the height (m2). Waist and hip circumference (to the nearest centimetre) was measured with a Gulick II spring-loaded measuring tape (Gay Mills, WI). The waist circumference was measured midway between the inferior angle of the last palpable rib and the suprailiac crest (1 inch above the navel due to pregnancy) and the hip circumference around the widest portion of the buttocks all with the tape parallel to the floor (Brown *et al.*, 1996). The ratio of the waist to hip circumference was calculated from the measured parameters. Only trained personnel took measurements of anthropometric variables.

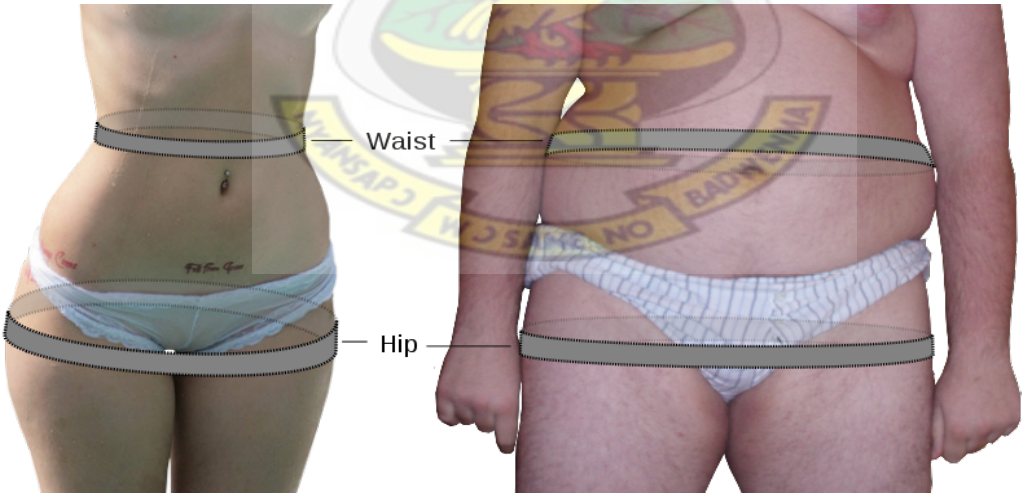


Figure 3-2 Measurement of waist to hip ratio in different body sizes. Source (Brown *et al.*, 1996)

3.5 MEASUREMENT OF VITAL SIGNS

3.5.1 Blood pressure

Blood pressure was measured (by trained personnel - Midwives) using a mercury sphygmomanometer and a stethoscope. Measurements were taken from the left upper arm after subjects had been sitting for >5 min in accordance with the recommendations of the American Heart Association (Kirkendall *et al.*, 1967). This was achieved when women were awaiting admission. Duplicate measurements were taken with a 5-minute rest interval between measurements and the mean value was recorded to the nearest 2.0 mmHg.

3.5.2 Temperature

The body temperature on admission was measured (by trained personnel - Midwives) with a digital Infrared ear thermometer (Calpol®). It is based on the principle of measurement of the infrared energy emitted from the eardrum in a calibrated length of time. It has been found to be a clinically reliable indicator of body core temperature, as the eardrum is located close to the hypothalamus, which is the body's temperature regulator. It however has the limitation of operator technique and quality of instrumentation. (Smitz *et al.*, 2009).

3.5.3 Pulse

The pulse on admission was checked (by trained personnel - Midwives). It was done by placing the index and middle fingers on the underside of the wrist, below the thumb to palpate the radial artery. The number of beats in 60 seconds was recorded as the pulse rate using a digital stopwatch.

3.6 SAMPLE COLLECTION AND PREPARATION

Approximately 9 mls of venous blood samples were collected upon recruitment. The BD Vacutainer® Safety-Lok™ blood collection set and the BD Vacutainer® Blood collection Tubes were used to ensure safety and accuracy in phlebotomy. The order of draw of blood was the sodium citrate tube for coagulation studies, the serum separator tube for biochemical assays and then the Ethylenediaminetetraacetic acid (EDTA) tube for haematological assays. The tourniquet (Sastedt Agent & Co.) was released as soon as blood draw began to reduce venous stasis.

Coagulation studies: 1.8 mls of venous blood was drawn into the BD Vacutainer™ 0.109M Glass Sodium Citrate tubes and inverted gently 3-4 times to mix. The sample was centrifuged at 2,500 xg for 15 minutes at 25^{o}C soon after blood collection. The plasma was aspirated with a plastic Pasteur pipette and stored in 1.8ml plastic CyroPure tubes (Sastedt Agent & Co.) at -80^{o}C until assayed.

Biochemical assays: About 3 mls of blood was drawn into the BD Vacutainer® SST™ II Advance tubes and inverted gently 4-5 times to mix with clot activator. The sample was allowed to form a dense clot for a minimum of 30 minutes in a vertical position and centrifuged at 2,000 xg for 10 minutes at 25^{o}C. Aliquots of the serum were stored in 1.8ml plastic CyroPure tubes (Sastedt Agent & Co.) at -80^{o}C until assayed.

Haematological assays: About 4 mls of blood was drawn into the BD Vacutainer® EDTA tubes containing 2.5 μg K2 EDTA as anticoagulant. The sample was mixed by gentle inversion 8-10 times. All assays were done soon after sample collection.

3.7 BIOCHEMICAL ASSAYS

Serum clinical biochemistry was performed on the Selectra Pro S System (Elitech Clinical Systems-Elitech Group). Parameters that were determined include: liver function tests – Total Protein (TP), Albumin (ALB), globulin, Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST); renal function tests – Urea (URE) and Creatinine (CRE). The URE/CRE ratio was calculated from the formula, URE (mmol/l)/CRE (mmol/l). The methods adopted by the automated equipment are as follows and all reagents were from Vital Scientific (Elitech Group). Commercially prepared control sera were used in quality control of the equipment before each batch of assay was run.

3.7.1 Total protein (Biuret)

The present method is based on the modification of an old method (Gornall *et al.*, 1949). Protein in serum forms a blue coloured complex in the presence of copper salt in an alkaline solution. The intensity of the violet colour at 546 nm is proportional to the amount of protein present when compared to a solution with known protein concentration.

$$\textit{Protein} + Cu^{2+} \xrightarrow{\textit{Alkali}} \textit{Coloured Complex}$$

3.7.2 Albumin (BCG)

At a controlled pH, bromocresol green (BCG) forms a coloured complex with ALB. The intensity of colour at 630 nm is directly proportional to ALB content (Doumas *et al.*, 1971)

$$\textit{BCG} + \textit{Albumin} \xrightarrow{\textit{controlled pH}} \textit{Green BCG /Albumin Complex}$$

3.7.3 Aspartate aminotransferase (AST)

The method is based on a kinetic IFCC method, without pyridoxal phosphate at 365 nm. AST levels present in the sample leads to the formation of oxaloacetate from L-Aspartate and α-Ketogluterate which reacts with Nicotinamide Adenine Dinucleotide (NADH) in the presence of (Malate Dehydrogenase) MDH to form L-Malate (Tietz, 1995).

$$\textit{L-Aspartate} + \alpha\textit{-Ketogluterate} \xrightarrow{\textit{AST}} \textit{oxaloacetate} + \textit{L-Glutamate}$$

$$\textit{Oxaloacetate} + \textit{NADH} + H^+ \xrightarrow{\textit{MDH}} \textit{L-Malate} + NAD^+$$

3.7.4 Alanine aminotransferase (ALT)

The method is based on a kinetic IFCC method, without pyridoxal phosphate at 365 nm. ALT levels present in the sample leads to the formation of pyruvate from L-Alanine and α-Ketogluterate which reacts with Nicotinamide Adenine Dinucleotide (NADH) in the presence of Lactate Dehydrogenase (LDH) to form L-Lactate (Tietz, 1995).

$$\textit{L-Alanine} + \alpha\textit{-Ketogluterate} \xrightarrow{\textit{ALT}} \textit{Pyruvate} + \textit{L-Glutamate}$$

$$\textit{Pyruvate} + \textit{NADH} + H^+ \xrightarrow{\textit{LDH}} \textit{L-Lactate} + NAD^+$$

3.7.5 Globulins

In human plasma ALB accounts for 50 to 60% of total proteins with the remaining fraction mainly containing globulins. The total globulin fraction is generally determined by subtracting the ALB from the TP. Any increase or decrease in the globulin fraction is best evaluated by serum electrophoresis (Busher, 1990).

3.7.6 Urea

Urea in serum is widely used as a screening test for renal function. It is usually used in conjunction with serum CRE to make a differential diagnosis in azotemia (pre-renal, renal and post-renal).

Urea is hydrolyzed in the presence of water and urease to produce ammonium and carbonate ions. The ammonium reacts with α-Ketogluterate in the presence of NADH to yield glutamate. Meanwhile, an equimolar quantity of NADH undergoes oxidation during the reaction catalyzed by Glutamate dehydrogenase (GLDH) resulting in a decrease in absorbance (340 nm) that is directly proportional to the urea nitrogen concentration in the sample (Tietz, 1995).

$$Urea + 2H_2O \xrightarrow{Urease} 2NH_4^+ + CO_3^{2-}$$

$$NH4^+ + \alpha\text{-}Ketogluterate + NADH \longrightarrow L\text{-}Glutamate + NAD^+ + H_2O$$

3.7.7 Creatinine

Creatinine is the waste spontaneous product of creatine metabolism. It is an excellent marker of renal function. Elevated creatinine levels are found in renal diseases and insufficiency with decreased glomerular filtration and in muscle dystropy and atropy.

The method is based on a modified Jaffe-Kinetic technique, which is very fast with very little interferences from proteins and carbohydrates. Creatinine reacts with an alkaline picric acid to form a coloured complex (yellow-orange). The rate of formation of colour is proportional to the creatinine in the sample at 505 nm (Tietz, 1995).

$$Creatinine + Alkaline\ Picrate \longrightarrow Creatinine\text{-}Picrate\ complex$$

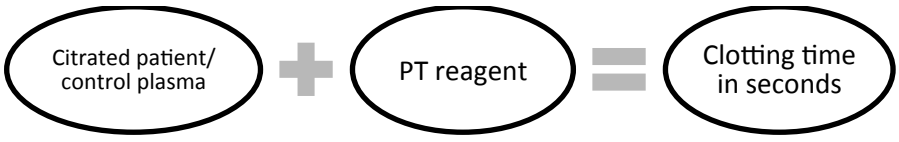
3.8 COAGULATION STUDIES

Coagulation studies on citrated plasma were done by manual methods as per the manufacturer's protocol. Parameters measured were PT and APTT. Reliability of test results was monitored within each run, using normal and abnormal control plasmas (Fortress Control Plasmas 1, 2 and 3). Samples were run in duplicates and the mean clotting time of duplicate samples and controls recorded (accepted values had differences less than 5%). The principles employed in the assays are as follows with reagents from Fortress Diagnostics Limited (United Kingdom).

3.8.1 Prothrombin Time (PT)

The PT is the fundamental screening test for acquired or inherited bleeding disorders and for monitoring oral anticoagulation therapy. The test is used for quantitative determination of blood clotting factors in the extrinsic (VII) and common pathways (II, V and X) of coagulation. The International Normalised Ratio (INR) was calculated using the following formula: INR = (Patient PT / Mean Normal PT) ^{ISI} (Biggs and Rizza, 1984; Hirsh, 1992).

The PT reagent (rabbit brain thromboplastin, calcium chloride, buffer, and 0.05% sodium azide) was added to citrated patient/control plasma, which activated the extrinsic clotting pathway. The clotting time was recorded in seconds. Test was conducted strictly according manufacturer's protocol.



3.8.2 Activated Partial Thromboplastin Time (APTT)

The APTT is used as a general screening test for the detection of coagulation abnormalities in the intrinsic pathway. The APTT is sensitive to deficiencies or abnormalities of factors VIII, IX, XI, XII, X and II, prekallikrein, HMWK and fibrinogen. The test is also sensitive to inhibitors of blood coagulation such as lupus inhibitor and fibrin/fibrinogen degradation products. The APTT is the most widely used method for monitoring intravenous heparin anticoagulation therapy (Biggs and Rizza, 1984; Hirsh, 1992).

The APTT reagent (rabbit brain cephalin and ellagic acid activator) was added to citrated patient/control plasma. Calcium chloride was then added which started the intrinsic pathway. The clotting time was recorded in seconds. Test was conducted strictly according manufacturer's protocol.

3.9 HAEMATOLOGICAL PARAMETERS

3.9.1 Full/Complete blood count (FBC)

Various haematological parameters including White Blood Cells (WBC), Lymphocytes (LYM), Monocytes (MONO), Eosinophils (EO), Basophils (BASO), Neutropils (NEUT), Red Blood Cells (RBC), Haemoglobin (HGB), Haematocrit (HCT), Mean Cell Volume (MCV), Mean Cell Haemoglobin (MCH), Mean Corpuscular Haemoglobin Concentration (MCHC), Red Cell Distribution Width (RDW), Platelets (PLT) and Mean Platelet Volume (MPV) were determined by an automated blood analyzer, SYSMEX XT 2000i. The WBC count was determined by flow cytometry using forward-scattered and side-scattered light. The differential

WBC uses a specific nucleic acid dye to measure the cells by side-fluorescent light and side-scattered light. The RBC and PLT impedance (I) were measured using direct-current detection. The HCT was simultaneously determined using the RBC pulse-height detection method. The following parameters were calculated from directly measured data MCV, MCH, MCHC, RDW by standard deviation, RDW by coefficient of variation (RDW-CV), platelet distribution width (PDW), mean platelet volume (MPV) and platelet large cell ratio (P-LCR) (Langford *et al.*, 2003).

3.9.2 The Erythrocyte Sedimentation Rate (ESR)

ESR is a non-specific test used in a wide range of infectious, inflammatory, degenerative, and malignant conditions associated with changes in plasma proteins. (Cheesbrough, 2006).

Principle and method of test

Citrated blood in a pippette was vertically positioned and left undisturbed for an hour, after which the rate of fall in mm/hr was recorded. The red cells aggregate and stick together to form rouleaux, which sediments through plasma. In normal whole blood, RBCs do not form rouleaux; the RBC mass is small and therefore the ESR is decreased (cells settle out slowly). The ESR is directly proportional to the RBC mass and inversely proportional to plasma viscosity (Cheesbrough, 2006).

3.9.3 Glucose-6-Phosphate Dehydrogenase (G6PD)

G6PD is involved in the generation of phosphorylated nicotinamide-adenine dinucleotide (NADPH) in the pentose phosphate pathway (hexose monophosphate shunt). NADPH is needed to provide glutathione (GSH) which maintains HGB and other red cell proteins in a reduced active form (Cheesbrough, 2006).

Principle and method of test

1ml each of anticoagulated (EDTA) blood was pippetted into three test tubes labelled as test (T), positive (P) and negative (N) control.

To the "P" and "T" tubes, 50 ul of sodium nitrite with glucose solution was added. To the "T" tube again, 50 ul of methylene blue was added. Nothing was added to the N tube. All tubes were corked and incubated at 37°C for 3hr with intermittent mixing at 1hr intervals.

HGB is oxidized to methaemoglobin (Hi) by sodium nitrite. The redox dye, methylene blue activates the pentose phosphate pathway, resulting in the enzymatic conversion of Hi back to HGB in those red cells with normal G6PD activity. In G6PD deficient cells there is no enzymatic reconversion to HGB. A charcateristic brown colour in the "T" tube which compared to the "P" tube was regarded as defective and that which compared to the "N" tube was regarded non-defective (Cheesbrough, 2006).

3.9.4 Sickle cell slide test

This is a simple test that does not differentiate between sickle cell disease and sickle cell trait.

Principle and method of test

Blood was mixed on a slide with a chemical reducing agent (sodium metabisulphite or sodium dithionite), covered with a cover glass, and incubated at room temperature for about 20 minutes to 1 hour. The reducing agent deoxygenates the HGB in the red cells providing the conditions for cells containing Haemoglobin S (HbS) to sickle. Slides were observed under ×40 magnification lens of a light microscope for charcteristic sickle-shaped red cells (Cheesbrough, 2006).

3.9.5 ABO blood group and Rh "D" status

The ABO and Rh grouping technique was employed. Fresh particpant blood cells were washed in saline to remove all blood grouping specific interfering substances before test was performed. A final 3-5% cell suspension was prepared and a 1:1 volume of patient red cells and Anti A, B and D monoclonal sera was prepared. The mixture was centrifuged at low speed of 150g for about 30 seconds. The contents of the tube were mixed gently and agglutinations observed (Cheesbrough, 2006).

3.9.6 Blood film (Thick and thin)

Thick and thin blood films were prepared on a new, clean grease free slide with single frosted ends. Both films were prepared on a single slide with the thin film about one-third distance from the non-frosted. The portion of the thin film was immersed in a coupling jar with absolute methanol for 30 seconds and allowed to air-dry completely. The smears were stained with a 5% giemsa stain for about 30 minutes and observed under ×100 oil immersion lens of a light microscope.

3.10 CUT OFFS AND REFERENCE INTERVALS

All references used for laboratory tests are ranges with respect to pregnancy to accommodate for all physiological changes (Tran, 2005; Abbassi-Ghanavati *et al.*, 2009).

BMI was classified as underweight (<18.5), normal (18.5 - <25), overweight (>25 - <30) and obese (>30) (WHO, 2004). Appropriate Waist to Hip Ratio (WHR) was defined as ≤0.8 (NIDDK).

URE/CRE ratios of <40 were classified as intra-renal, >100 as pre-renal and 40-100 as normal (Rachoin *et al.*, 2012).

3.11 DIAGNOSTIC CRITERIA AND DEFINITION

Diagnosis of primary PPH was based on the following criteria:

•Vaginal delivery with a measured blood loss of 500mL or more within the first 24hours.

•Vaginal delivery with a measured blood loss of less than 500mL but enough to cause haemodynamic shock; within the first 24 hours (Naz *et al.*, 2008; NSW, 2010).

3.11.1 Measurement of blood loss

A qualified Midwife measured blood loss with a graduated wedge-shaped receptacle. Deliveries were done on a "linen saver." The amniotic fluid was allowed to drain away and blood was allowed to collect into the receptacle. The midwives did a visual estimation of the blood loss and accurate measurement was also taken from the receptacle graduations. This was to enable a proper comparison of the two different diagnostic methods.

3.12 STATISTICAL ANALYSIS

All categorical variables were compared with Chi-square or Fisher's exact test based on the sum of the values in each cell used for the analysis. Fisher's exact was used for variables with cells less than 5 and Chi-square for those with more than 5.

All continuous variables were analysed based on the distribution of the variables

Medians (also equivalent to the logarithm means) were determined for skewed data and means for normally distributed data.

Differences in two medians were analysed using Wilcoxon-Mann-Whitney (Rank sum) test and Independent samples t-test was used to compare the difference between means.

A Receiver Operating Characteristic (ROC) curve was used to compare the accuracy of visual estimation as a measure of blood loss in the diagnosis of primary PPH.

Multivariate analysis was done to identify independent risk factors associated with primary PPH. Several variable predictors were tested against the cases and controls using a logistic regression model. Independent risk factors were identified using an automatic selection process (MODELSTEP), which removes non-significant variables and confounders in a stepwise backward selection process, based on likelihood ratio static. An Akaike's Information Criterion (AIC) is constantly generated and the last MODELSTEP with the smallest AIC was selected as the best model to fit.

Chapter 4

RESULTS

Table 4.1 Socio-demographic parameters of study participants.

PARAMETERS	ALL WOMEN (n=271)	CASES (n=55)	CONTROLS (n=216)	P VALUE
AGE (YRS)				
Mean *(SD)*	27.7 (5.7)	27.9 (6.3)	27.7 (5.5)	0.27
0-19 *n (%)*	20 (7.4)	3 (5.5)	17 (7.9)	
19-29 *n (%)*	161 (59.4)	32 (58.2)	129 (59.7)	
29-39 *n (%)*	85 (31.4)	18 (32.7)	67 (31.0)	
39-49 *n (%)*	5 (1.8)	2 (3.6)	3 (1.4)	0.618
ETHNICITY *n (%)*				
AKAN	195 (72)	35 (63.6)	160 (74.1)	
GA-ADAMGBE	2 (0.7)	1 (1.8)	1 (0.5)	
MOLE-DAGBANI	72 (26.6)	18 (32.7)	54 (25.0)	
YORUBA	2 (0.7)	1 (1.8)	1 (0.5)	0.149
EDUCATIONAL LEVEL *n (%)*				
ILLITERATE	31 (11.4)	4 (7.3)	27 (12.5)	
JHS	135 (49.8)	30 (54.5)	105 (48.6)	
PRIMARY	43 (15.9)	8 (14.5)	35 (16.2)	
SHS	34 (12.5)	9 (16.4)	25 (11.6)	
TERTIARY	28 (10.3)	4 (7.3)	24 (11.1)	0.582
OCCUPATION *n (%)*				
ADMINISTRATIVE	3 (1.1)	0 (0)	3 (1.4)	
AGRICULTURAL	7 (2.6)	2 (3.6)	5 (2.3)	
EDUCATIONAL	13 (4.8)	2 (3.6)	11 (5.1)	
STUDENT	12 (4.4)	2 (3.6)	10 (4.6)	
TRADING	142 (52.4)	29 (52.7)	113 (52.3)	
UNEMPLOYED	54 (19.9)	29 (52.7)	44 (20.4)	
VOCATIONAL	40 (14.8)	10 (18.2)	30 (13.9)	0.961
MARITAL STATUS *n (%)*				
MARRIED	191 (70.5)	41 (74.5)	150 (69.4)	
SINGLE	80 (29.5)	14 (25.5)	66 (30.6)	0.565

Data above is presented in mean (SD) or *n* (%). All P values less than 0.05 are considered significant. Cases: Women with primary PPH. Controls: Women without primary PPH. SD: Standard Deviation. JHS: Junior High School. SHS: Senior High School. n: Number

Table 4.1 shows the socio-demographic distribution of the study participants. The prevalence of primary PPH in the current study was 15.8%. The mean age of participants was 27.7±5.7 years and ages of women with and without primary PPH were not significantly different (P=0.27). Women were mainly of the Akan ethnicity (72%) with a few Mole-Dagbani's (26.6%) and sparse Ga-Adangbe's and Yoruba's (0.7% each). Ethnicity however did not differ significantly among the cases and controls. Overall, most of the women were literate, with close to half (49.8%) having at least basic education. Education, occupation and marital status did not differ significantly between the two groups.

Table 4.2 Clinical and obstetric history of study participants.

PARAMETERS	ALL WOMEN (n=271)	CASES (n=55)	CONTROLS (n=216)	P VALUE
PARITY				
Median *(IQR)*	1 (0,2)	1 (0,3)	1 (0,2)	0.46
NULLIPAROUS *n (%)*	105 (38.7)	21 (38.2)	84 (38.9)	
PRIMIPARA *n (%)*	63 (23.2)	12 (21.8)	51 (23.6)	
MULTIPARA *n (%)*	103 (38)	22 (40)	81 (37.5)	0.933
SPONTANEOUS BLEEDING *n (%)*				
NO	257 (94.8)	51 (92.7)	206 (95.4)	0.493
YES	14 (5.2)	4 (7.3)	10 (4.6)	
REGULAR PERIODS *n (%)*				
NO	6 (2.2)	3 (5.5)	3 (1.4)	0.1
YES	265 (97.8)	52 (94.5)	213 (98.6)	
ANTEPARTUM BLEEDING *n (%)*				
NO	257 (94.8)	53 (96.4)	204 (94.4)	0.742
YES	14 (5.2)	2 (3.6)	12 (5.6)	

PARAMETERS	ALL WOMEN (n=271)	CASES (n=55)	CONTROLS (n=216)	P VALUE
INDUCED ABORTIONS ***n (%)***				
NO	162 (59.8)	35 (63.6)	127 (58.8)	0.617
YES	109 (40.2)	20 (36.4)	89 (41.2)	
SPONTANEOUS ABORTIONS ***n (%)***				
NO	214 (79)	44 (80)	170 (78.7)	0.98
YES	57 (21)	11 (20)	46 (21.3)	
TRANSFUSION ***n (%)***				
NO	252 (93)	50 (90.9)	202 (93.5)	0.553
YES	19 (7)	5 (9.1)	14 (6.5)	
SURGERY ***n (%)***				
NO	227 (83.8)	47 (85.5)	180 (83.3)	0.86
YES	44 (16.2)	8 (14.5)	36 (16.7)	
FIBROIDS ***n (%)***				
NO	267 (98.5)	53 (96.4)	214 (99.1)	0.184
YES	4 (1.5)	2 (3.6)	2 (0.9)	
PPH ***n (%)***				
NO	253 (93.4)	50 (90.9)	203 (94.0)	0.377
YES	18 (6.6)	5 (9.1)	13 (6.0)	
CONTRACEPTIVE USE ***n (%)***				
NO	218 (80.4)	48 (87.3)	170 (78.7)	0.215
YES	53 (19.6)	7 (12.7)	46 (21.3)	
HERBAL PREPARATIONS				
NO	155 (57.2)	30 (54.5)	125 (57.9)	0.77
YES	116 (42.8)	25 (45.5)	91 (42.1)	
ENEMA PRACTICE ***n (%)***				
NO	180 (66.4)	34 (61.8)	146 (67.6)	0.516
YES	91 (33.6)	21 (38.2)	70 (32.4)	

Data above is presented in *n* (%) or median (IQR). All P values less than 0.05 are considered significant. Cases: Women with primary PPH. Controls: Women without primary PPH. SD: Standard Deviation. IQR: Inter-quartile range. *n:* Number

Table 4.2 shows the clinical and obstetric history of the study population, cases and controls. Primiparous women were the least parity classification group (23.2%) with an almost equal distribution between nulliparous and multiparous women. Parity however did not differ significantly between PPH and non-PPH controls. Majority of the women had not had, spontaneous bleeding of any kind (94.8%), antepartum bleeding, (94.8%), spontaneous abortions (79%), blood transfusions (93%), surgery (83.8%), fibroids (98.5%) and history of PPH (93.4%). Number of women without antepartum bleeding (96.4%), induced and spontaneous abortions (63.6%; 80%), history of surgery (85.5%) and contraceptive use (87.3%) was highest amongst the cases but this was not significant.

Table 4.3 Anthropometric variables of study participants.

PARAMETERS	ALL WOMEN (n=271)	CASES (n=55)	CONTROLS (n=216)	P VALUE
WEIGHT (kg) *median (IQR)*	70 (61,79)	70 (61.5,82)	70 (61,79)	0.822
HEIGHT (cm) *median (IQR)*	160 (156.2,165)	160 (156,165.2)	161 (157,165)	0.766
BMI				
Median *(IQR)*	25 (24,28)	26 (24,30.5)	25 (24,28)	0.092
NORMAL *n (%)*	155 (57.4)	26 (48.1)	129 (59.7)	
OVERWEIGHT *n (%)*	72 (26.7)	14 (25.9)	58 (26.9)	
OBESE *n (%)*	43 (15.9)	14 (25.9)	29 (13.4)	0.072
WHR				
Median *(IQR)*	1 (1,1.1)	1 (1,1.1)	1 (1,1.1)	0.417
NORMAL *n (%)*	4 (1.5)	1 (1.8)	3 (1.4)	
HIGH *n (%)*	267 (98.5)	54 (98.2)	13 (98.6)	1
TEMPERATURE (°C) median *(IQC)*	36.2 (35.6,36.5)	36.2 (35.6,36.5)	36.1 (35.7,36.5)	0.581
SBP (mmHg)				
Median *(IQR)*	110 (110,120)	120 (110,128)	110 (106,120)	0.005
NORMAL *n (%)*	265 (97.8)	54 (98.2)	211 (97.7)	
HYPERTENSIVE *n (%)*	6 (2.2)	1 (1.8)	5 (2.3)	1
PULSE (bpm) *median (IQR)*	90 (81,96)	90 (81.5,93)	89.5 (80.8,97)	0.963

Data above is presented in *n* (%) or median (IQR). All P values less than 0.05 are considered significant. Cases: Women with primary PPH. Controls: Women without primary PPH. IQR: Inter-quartile range. *n*: Number. BMI: Body Mass Index. WHR: Waist to Hip Ratio.

Table 4.3 shows anthropometric variables of the study population, cases and controls. The current study showed a median weight of 70Kg, a height of 160cm with a BMI of 25. Median WHR was 1.0 and majority of the participants had a high

WHR (98.5%). Median SBP was 110mmHg with that of the cases (120mmHg) significantly higher than that of the non-PPH controls (110mmHg).

Table 4.4 Biochemical and coagulation parameters of study participants.

PARAMETERS	ALL WOMEN (n=271)	CASES (n=55)	CONTROLS (n=216)	P VALUE
AST *median (IQR)*	17 (13.5,21)	18 (15,22.5)	16 (13,20)	**0.043**
ALT *median (IQR)*	9 (6,11)	8 (6.5,11)	9 (6,11)	0.48
TP *median (IQR)*	68 (63,73)	66 (59.5,74)	68 (63,73)	0.315
ALB *median (IQR)*	36 (34,38)	35 (31.5,38)	37 (35,39)	**0.001**
GLOB *median (IQR)*	30 (28,34)	31 (27.5,36)	30 (28,34)	0.889
URE *median (IQR)*	1.8 (1.5,2.4)	2.5 (1.8,3.2)	1.8 (1.5,2.3)	**< 0.001**
CRE *median (IQR)*	66 (52.5,78.5)	72 (61,90.5)	61.5 (51,75.2)	**0.002**
URE: CRE				
Median *(IQR)*	28 (22,38)	31 (24,45)	27 (21,36.8)	0.014
INTRARENAL *n (%)*	217 (80.7)	35 (63.6)	182 (85.0)	
NORMAL *n (%)*	50 (18.6)	18 (32.7)	32 (15.0)	
PRE-RENAL *n (%)*	2 (0.7)	2 (3.6)	0 (0)	**< 0.001**
PT *median (IQR)*	13 (12,15)	14 (13,16)	13 (12,15)	0.096
INR *median (IQR)*	1.1 (1,1.3)	1.2 (1.1,1.4)	1.1 (1,1.3)	0.096
APTT *median (IQR)*	28 (24,36)	31 (24,38)	28 (24.8,33.5)	0.576

Data above is presented in *n* (%) or median (IQR). All P values less than 0.05 are considered significant. Cases: Women with primary PPH. Controls: Women without primary PPH. IQR: Inter-quartile range. n: Number. AST: Aspartate aminotransferase. ALT: Alanine aminotransferase. TP: Total Protein. ALB: Albumin. URE: Urea. CRE: Creatinine. PT: Prothrombin Time. APTT: Activated Partial Throboplastin Time. INR: International Normalised Ratio.

Table 4.4 shows a list of biochemical and coagulation parameters of the study population, primary PPH cases and non-PPH controls. AST (P=0.043), URE (P<0.001) and CRE (P=0.002) levels were higher in women who developed primary PPH than those who did not. URE: CRE ratios significantly differed between the two groups with the cases having a higher value. Statistically, ALB levels were higher among the control group compared to those with primary PPH (P=0.001). Measures of coagulation; PT and its corresponding INR was not different statistically between the two groups compared but was appreciable.

Table 4.5 Haematological parameters of study population.

PARAMETERS	ALL WOMEN (n=271)	CASES (n=55)	CONTROLS (n=216)	P VALUE
HGB (g/dL) *median (IQR)*	11.9 (10.9,12.8)	10.7 (8.5,12.3)	12.1 (11.3,13)	**< 0.001**
ANAEMIA *n (%)*				
MOD-SEV	36 (13.3)	22 (40)	14 (6.5)	
MILD	37 (13.7)	9 (16.4)	28 (13)	
NORMAL	198 (73.1)	24 (43.6)	174 (80.6)	**< 0.001**
G6PD *n (%)*				
FULL DEFECT	12 (4.4)	0 (0)	12 (5.6)	
NO DEFECT	257 (94.8)	55 (100)	202 (93.5)	
PARTIAL DEFECT	2 (0.7)	0 (0)	2 (0.9)	0.169
SICKLING *n (%)*				
NEGATIVE	235 (86.7)	47 (85.5)	188 (87.0)	
POSITIVE	36 (13.3)	8 (14.5)	28 (13.0)	0.931
BLOOD GROUP *n (%)*				
AB Rh D POS	4 (1.5)	2 (3.6)	2 (0.9)	
A Rh D NEG	6 (2.2)	2 (3.6)	4 (1.9)	
A Rh D POS	62 (22.9)	6 (10.9)	56 (25.9)	
B Rh D NEG	12 (4.4)	6 (10.9)	6 (2.8)	
B Rh D POS	46 (17)	6 (10.9)	40 (18.5)	
O Rh D NEG	11 (4.1)	0 (0)	11 (5.1)	
O Rh D POS	130 (48)	33 (60)	97 (44.9	**0.002**
HCT *median (IQR)*	36.1 (32.9,38.5)	32.1 (25.2,36.8)	36.5 (33.6,38.5)	**< 0.001**
MCV *median (IQR)*	84.8 (80.5,88.6)	85.9 (81.6,88.2)	84 (80.1,88.7)	0.426
MCH *median (IQR)*	28.1 (26.9,29.7)	29 (27.4,30.1)	28.1 (26.8,29.6)	0.151
MCHC *median (IQR)*	33.2 (32.6,34.3)	33.4 (32.8,34.3)	33.2 (32.6,34.3)	0.248
PLT *mean (SD)*	205.8 (66.8)	210 (69.3)	204.7 (66.2)	0.597

PARAMETERS	ALL WOMEN (n=271)	CASES (n=55)	CONTROLS (n=216)	P VALUE
WBC *median (IQR)*				
Total	9.4 (7.4,12.9)	10.2 (8.8,15)	9.4 (7.1,12.5)	**0.023**
NEUT	7.3 (5.1,11)	8.6 (6,12.9)	7 (4.8,9.8)	**0.004**
LYMPH	1.5 (1.2,2)	1.6 (1.2,1.9)	1.5 (1.2,2)	0.831
MONO	0.7 (0.6,0.9)	0.8 (0.5,1.2)	0.7 (0.6,0.9)	**0.017**
EO	0 (0,0.1)	0 (0,0.1)	0 (0,0.1)	0.116
BASO	0 (0,0)	0 (0,0)	0 (0,0)	0.119
ESR (mm/hr) *median (IQR)*	56 (39.5,76)	70 (48,96)	55 (37,75)	**0.018**
MALARIA PARASITES *n (%)*				
NEGATIVE	254 (93.7)	51 (92.7)	203 (94)	
POSITIVE	17 (6.3)	4 (7.3)	13 (6)	0.756
BLOOD FILM PICTURE *n (%)*				
ABNORMAL	99 (36.5)	39 (70.9)	60 (27.8)	
NORMAL	172 (63.5)	16 (29.1)	156 (72.2)	**< 0.001**

Data above is presented in *n* (%) or median (IQR) or mean (SD). All P values less than 0.05 are considered significant. Cases: Women with primary PPH. Controls: Women without primary PPH. IQR: Inter-quartile range. *n*: Number. HGB: Haemoglobin. G6PD: Glucose-6-Phosphate Dehydrogenase. HCT: Haematocrit. MCV: Mean Cell Volume. MCH: Mean Cell Haemoglobin. MCHC: Mean Corpuscular Haemoglobin Concentration. PLT: Platelets. WBC; White Blood Cell. NEUT: neutrophils. LYPH: Lymphocyte. MONO: Monocytes. EO: Eosinophil. BASO: Basophil. ESR: Erythrocyte Sedimentation Rate. POS: Positive. NEG: Negative. Rh: Rhesus factor.

Table 4.5 shows a set of haematological parameters of the study population, PPH and non-PPH controls. Median HGB of study participants was 11.9g/dL and women with primary PPH had a significantly lower HGB (10.7g/dL) compared to 12.1g/dL in non-PPH controls. Most of the women had a normal HGB level (73.1%) with respect to anaemia classification (WHO, 1989) with better levels among non-PPH controls (P<0.001) when compared with primary PPH cases. All grades of anaemia were more amongst primary PPH cases compared to controls (P<0.001). Blood group O Rh "D" positive was the predominant blood type among the study population. Distribution in blood group was however statistically different between the two groups with the cases generally exhibiting more variations. WBC level was higher among PPH cases compared to controls (P=0.023) with NEUT and MONO levels higher amongst the former. ESR levels were generally high (56mmfall/hr) and PPH cases had a significantly higher ESR (70mmfall/hr) when compared to the control group (55mmfall/hr; P=0.018). Most of the women had a normal blood film picture but more of the women with primary PPH had an abnormal picture (P<0.001) with a variety of characteristics and conditions observed. A vast majority of the women studied tested negative for malaria infection (93.7%).

Table 4.6 Comparison of direct calibrated measurement to visual estimation as measures of blood loss during delivery.

PARAMETERS	MEASURED	VISUAL ESTIMATION	P VALUE
OBSERVATIONS *(n)*	271	271	
SD	218.39	188.78	
MINIMUM VOLUME *(ml)*	50	100	
MAXIMUM *VOLUME* *(ml)*	1050	900	
MEAN *(ml)*	306.089	250.406	
BIAS *(ml) mean* ± SD	55.68266 ± 47.3384		
AREA UNDER CURVE	**0.6104**		**< 0.0001**
STANDARD ERROR	0.02413		

Data is presented in mean ± SD. All P values less than 0.05 are considered significant. SD: Standard deviation. *n*: Number

Table 4.6 shows a comparison of the direct calibrated measurement with visual estimation as measures of blood loss in the diagnosis of primary PPH. As with the total number of participants studied, 271 observations were made. When both methods were compared, the mean blood loss for calibrated measurement was 306.089mls opposed to 250.406mls in visual estimation with a bias of 55.6827 ± 47.3384 (P<0.0001). Visual estimation gave a prevalence of 12.35% as opposed to the 15.8% in direct measurement; an underestimation of 3.5%. When compared to direct calibrated measurement, visual estimation gave an area of 0.6104, confirming an underestimation by the method and thus making it unsuitable for blood loss estimation.

Table 4.7 Multivariate logistic regression for independent variables.

PARAMETERS	Crude OR (95%CI)	Adj. OR (95%CI)	P value (Wald's test)	P value (LR-test)
SBP	1.03 (1.01,1.06)	1.03 (1,1.06)	0.094	0.095
BLOOD GROUP (ref=AB POS)				
A Rh D NEG	0.5 (0.04,6.68)	0.24 (0.01,5.28)	0.366	
A Rh D POS	0.11 (0.01,0.94)	0.04 (0,0.56)	**0.017**	
B Rh D NEG	1 (0.1,9.61)	0.42 (0.03,6.3)	0.53	
B Rh D POS	0.13 (0.01,1.09)	0.02 (0,0.35)	**0.007**	
O Rh D POS	0.34 (0.05,2.51)	0.11 (0.01,1.38)	0.087	**< 0.001**
CRE	1.02 (1.01,1.04)	1.05 (1.02,1.07)	**< 0.001**	**< 0.001**
URE: CRE (normal vrs intrarenal)	3.35 (1.72,6.52)	4.81 (1.68,13.76)	**0.003**	**0.003**
ANAEMIA (ref= MOD-SEV)				
MILD	0.18 (0.06,0.49)	0.22 (0.07,0.74)	**0.014**	
NORMAL	0.07 (0.03,0.16)	0.07 (0.02,0.21)	**< 0.001**	**< 0.001**
BLOOD FILM (ref = Normal)	0.16 (0.09,0.32)	0.4 (0.17,0.95)	**0.038**	**0.039**

SBP: Systolic Blood Pressure. Rh: Rhesus "D"factor. POS: Positive. NEG: Negative. CRE: Creatinine. URE: Urea. ref: Reference. OR: Odds ratio. Adj: Adjusted. CI: Confidence Interval. LR: Likelihood ratio Test. ref: Reference. MOD-SEV: Moderate–Severe. P values less <0.05 are considered significant.

Table 4.7 shows the logistic regression with crude and adjusted OR's for independent risk factors. From the table, blood group, CRE, URE: CRE, anaemia and blood film picture came out as independent factors associated with primary PPH.

For every one-unit increase in SPB, the log odds of primary PPH increases by 0.03 with the odds of developing primary PPH being 1.03 times higher in high SBP patients. This is however not significant but appreciable.

Using blood group AB Rh "D" POS as reference, A Rh "D" POS and B Rh "D" POS are significantly associated with primary PPH with an OR of 0.11 and 0.13

respectively. Hence participants with these blood groups were offered some form protection against the development of primary PPH.

CRE was found to be strongly associated with primary PPH. For every one-unit increase in CRE, the log odds of developing primary PPH increases by 0.045 and this is significant (P: <0.001). Thus the odds of developing primary PPH among high patients with high CRE is 1.05 times higher.

Furthermore for every one unit change in URE: CRE ratio the log odds of developing primary PPH increases significantly by 1.5 and the odds of developing primary PPH is 3.35 times more in those with increasing ratios.

With moderate-severe anaemia as reference, patients with mild anaemia conditions (≥10g/dl) and normal HGB levels are less likely to develop primary PPH (OR: 0.18; 0.07 respectively). Conversely, patients with a low HGB level are more likely to develop primary PPH and its severe forms.

An abnormal blood picture was not associated with the development of primary PPH (OR: 0.16). Thus an abnormal blood picture cannot be established as risk factor and should be assessed in contex of the patient, when predicting primary PPH development.

Chapter 5

DISCUSSION

The current study sought to determine and assess medical and haemato-biochemical parameters, their association and ability to predict the occurrence of primary PPH. The study also sought to evaluate visual estimation of blood loss as a method of diagnosing primary PPH.

The findings in the current study confirms our hypothesis that certain antepartum factors are associated with the occurrence of primary PPH, but only a few are predictive and may have utility for screening and assessment, and hence patient management strategies.

5.1 PREVALENCE OF PRIMARY PPH

The exact prevalence of primary PPH over the years has proven difficult to determine due to various challenges associated with blood loss estimation methods and hence the diagnosis of primary PPH (Willis and Livingstone, 1995; Ekeroma *et al.*, 1997).

In the current study, prevalence of primary PPH was 15.8%. This is relatively high as opposed to other studies conducted within the sub region. Contrary to this study, ranges between 5-12% of vaginal deliveries have been quoted (Willis and Livingstone, 1995; Ekeroma *et al.*, 1997), with some studies reporting even lower incidences of 1.68% (Ajenifuja *et al.*, 2010). In the study, Ajenifuja and colleagues attributed this very low incidence to the fact that AMTSL was practiced effectively with the use of oxytocics, which has been proven to reduce the incidence of primary PPH by up to 60%. However in most of these studies, blood loss was estimated and not measured. Two other studies have however confirmed the prevalence in the current study with a prevalence rate of as high as 18% of total

births worldwide (Dongol *et al.*, 2010) and an even higher 18.7% in Middle Africa (Carroli *et al.*, 2008). A closer but lower rate of 14.2% has also been recorded in Eastern Africa. (Carroli *et al.*, 2008). The high prevalence obtained in the current study could be attributed to a correction in the various challenges associated with the estimation of blood loss, the ultimate in the diagnosis of primary PPH. It is known that in Africa, similar or perhaps more challenges present with the estimation of blood loss and diagnosis of PPH, which leads to wide variations of prevalence across the continent (Willis and Livingstone, 1995; Ekeroma *et al.*, 1997). The definition of primary PPH states a cut-off blood loss of 500ml or more. This means that any amount of blood loss below this volume is tolerable and does not constitute PPH. However, this is not true as certain areas where prevalence of anaemia and hypertension in pregnancy is high, women who lose as little as about 250ml of blood may constitute a serious clinical problem (El-Refaey and Rodeck, 2003; NSW, 2010). Conversely, in the developed world, women may lose about this amount and face no significant morbidity. This is an indication that the definition does not take into account predisposing health conditions that reflect in the definition. In the case of the current study however, primary PPH was diagnosed by a Gynaecologist, as suggested in an article by Lalonde and colleagues in 2006. They stated that it is expedient for most health workers to take into account any amount of blood loss that causes signs of haemodynamic compromise rather than blood volumes (Lalonde *et al.*, 2006).

It has also been suggested that visual estimation of the exact amount of blood loss is subjective and hence there is no gold standard method for estimation in most facilities. This has posed a challenge to most facilities (Lalonde *et al.*, 2006; Ramanathan and Arulkumaran, 2006) and can lead to a gross underestimation of PPH by up to 50% (NSW, 2010).

The above done otherwise in our study, may be a contributing factor to the higher prevalence rate obtained. In support of this prevalence, PPH was the 5th highest cause of admissions and the 4th amongst the top 10 causes of maternal deaths at the Komfo Anokye Teaching Hospital in Kumasi (KATH, 2009). With limited data on the subject area in Ghana, more studies need to be conducted to add to this evidence.

5.2 ETHNICITY AND PRIMARY PPH

Almost all of the women recruited onto the study were of the Akan ethnicity. Hence the current study was not much multiethnic. This may be due to a bias created by the site of the study, Kumasi, Ashanti region. Most people who reside in this area are mostly Akan, hence the similarity between cases and controls (P=0.149). In contrast, other studies involving multiracial populations found the Asian race (OR=1.8) to be a risk factor (Magann *et al.*, 2005). Hence a much wider population based study may have to be conducted in order to determine the role of ethnicity in the development of primary PPH in Ghana.

5.3 OBSTETRIC HISTORY AND PRIMARY PPH

Most studies have found an association between multiparity and PPH over the years (Tsu, 1993). The current study however found no such associations. Similar studies have also revealed the same. Two of such studies found no relation between grand multiparity and significant obstetric haemorrhage (Stones *et al.*, 1993; Selo-Ojeme and Okonofua, 1997). Selo-Ojeme and his colleagues explained this finding as the efficacy of a policy targeted at multiparous women based on

previous literature, which established this as a risk factor. Thus the reduced episodes of primary PPH among the group they studied. A similar thing can be said for the current study as an efficient AMTSL or an elective cesarean section is practiced especially for this category of women and other suspected high-risk groups at the KATH, to ensure that no likely PPH episode occurs.

It is of interest that previous studies have reported prior episodes of PPH as an important risk factor to the development of subsequent episodes (Magann *et al.*, 2005), but the current study did not. Moreover, the elicitation of previous PPH in the current population may be difficult, as the number who reported PPH history was very small compared to the number who developed PPH. A similar finding was established in Nigeria (Selo-Ojeme and Okonofua, 1997), where in line with the current study, the educational standards of the study population was not high and thus many of them were probably not aware they had had PPH before. Moreover, with the estimation of blood loss being a great challenge (Willis and Livingstone, 1995; Ekeroma *et al.*, 1997), many of the women may have been near-miss PPH cases as blood losses may have been assumed to be within normal limits. We therefore recommend that history of PPH be objectively ascertained to establish it as risk factor.

5.4 BMI AND PRIMARY PPH

Studies have established that obese women are at a higher risk of intrapartum and postpartum complications, of which primary PPH forms a major part. Two of such ones, confirmed that obese women had an OR of 1.5 for PPH when compared to normal and overweight women (Usha *et al.*, 2005; Fyfe *et al.*, 2012). Furthermore, in-vitro studies of mymoetrial cells obtained during caesarean section showed that, dyslipidaemia and increased leptin levels reduce the contractile ability of the

myometrium and hence may predispose to primary PPH (Zhang *et al.*, 2007; Vinayagam and Chandraharan, 2012). However in these studies blood loss estimation was done visuslly, and opens these observations to bias. In support of the current study, a study conducted in the U.S.A where blood loss was measured revealed that for haemodynamic shock to occur, the amount of blood loss required is rather proportional to the woman's size and that increased BMI is not a risk factor for primary PPH (Hernandez *et al.*, 2012). Conversely, smaller women may loose very little blood to enter into shock and bigger women lose more blood before entering into shock. This is also supported in another recent study that has shown that a BMI ≥30 is associated with a reduced risk of severe PPH (Paglia *et al.*, 2012). Paglis and his colleagues showed that women with PPH were almost two times more likely to have a BMI <30 when results were controlled for ethnicity and mode of delivery. Another study conducted in the United Kingdom also showed no significant difference in BMI between PPH and non-PPH controls. There was also no significant difference in first and second stages of labour and retained products were also lower in obese women than women of normal weight. As such PPH was no different in all BMI groups (Arrowsmith *et al.*, 2011). These findings are in line with the fact that we could not find any differences or associations between BMI and primary PPH. We however recommend that BMI as a risk factor be considered in contex of specific populations.

5.5 BIOCHEMICAL PARAMETERS AND PRIMARY PPH

AST and ALB levels, although significantly differed between the two groups (ie > in cases) under study (P=0.043; P=0.001 respectively), were within normal limits and were not associated with odds of developing primary PPH on multivariate analysis. Therefore, they were not independent risk factors for primary PPH.

Higher levels of AST than ALT as well as differences among the current participants could be accounted for from other sources of the enzyme. Some of which are the heart, skeletal muscles, kidney, brain and red cells (Cheesbrough, 2006). Moreover, there was no concurrent trend with the more liver specific ALT levels among the participants. These go to confirm that there was basically no apparent liver dysfunction among the study participants. The exclusion of liver infection by screening participants for hepatitis B and C viral markers could be a contributing factor for normal liver function markers among the study participants. This is confirmed in a study where the selection of women was solely based on Hepatitis E infection. In this study, assessment of women with PPH also revealed simultaneous significant changes in the ALT, INR and D-dimer levels (Puri *et al.*, 2011). To the best of our knowledge data is limited in the area of liver function parameters in the prediction of primary PPH.

URE and CRE levels, including the ratio (URE: CRE) was significantly higher among women who developed PPH than non-PPH controls. Despite elevated levels of some coagulation factors in pregnancy (Ahonen *et al.*, 2010), bleeding may still occur, pointing to the fact that platelet abnormalities may be a cause of bleeding among such people (Collins *et al.*, 2011). Increasing urea levels causes reduced endothelial adhesion of platelets due to impaired VWF binding to platelets (Collins *et al.*, 2011). Hence this may be the case in the current study. CRE, a more sensitive marker of renal function was also an independent risk factor for primary PPH. Although levels were higher amongst the cases, it was still within normal limits. Since CRE is expected to decline in pregnancy (Tran, 2005; Abbassi-Ghanavati *et al.*, 2009), the increasing levels observed among the cases than controls is not likely to be due to renal impairment. This is observed in the impact the higher levels of CRE had in reducing the URE/CRE ratio. However eGFR was not determined for participants to exclude renal impairment. The significntly

higher CRE levels could however be attributed to muscular sources. There could be smooth muscle destruction (atrophy or dystrophy) of the uterus, conditions under which there is loss of muscle integrity and proteins, an impact on uterine preparedness for labour. A higher CRE level was associated with a higher likelihood to develop primary PPH (OR: 1.05; P: <0.001) and for every unit increase in CRE levels, the log odds of PPH increases by 0.045. There is also not much data on the relationship of renal markers and the development of primary PPH hence more work needs to be done to ascertain the finding in the current study.

5.6 COAGULOPATHY AND PRIMARY PPH

Measures of coagulation, PT and APTT did not differ between the two groups and hence showed no significant association. It is expected that bleeding tendencies will correlate with abnormalities in coagulation markers. The current study proved otherwise but was still in line with findings that coagulation abnormalities contribute only about 1% of the causes of PPH (Anderson *et al.*, 2000). It is important to note that coagulation abnormalities cannot be ruled out in this case. A hypercoagulable state results in the second and especially third trimesters due to an increased synthesis and activity of several coagulation factors. The amounts of fibrinogen, coagulation factors (F) VII, VIII, IX, X, XII, and VWF increase considerably. This also resulting in a shortened PT and APTT (Ahonen *et al.*, 2010). This could be a contributing factor to our finding of a relatively normal PT and APTT, which could be a pseudo-normal finding. Hence in the current study coagulation abnormalities may have been present, masked by physiological changes, and may be apparent only after pregnancy.

5.7 HAEMATOLOGICAL PARAMETERS AND PRIMARY PPH

HGB levels and thus anaemia was shown to be associated with primary PPH. Median HGB of the participants was generally within limits of pregnancy. However, women with PPH had a significantly lower HGB (10.7g/dL) compared to 12.1g/dL in non-PPH controls. Women with normal HGB levels and mild anaemia (HGB>10) were associated with an OR of 0.07 and 0.18 respectively. Hence women with HGB levels below this (HGB<10) are more likely to develop primary PPH, even with minor blood losses as this could lead to haemodynamic compromise. With the diagnostic definition employed in the current study, such was expected. Similar studies have shown that anaemia is estimated to be responsible for 17–46% of cases of maternal death when combined with obstetric haemorrhage (Carroli *et al.*, 2008) and that complications of PPH, pre-term delivery and foetal growth restriction are more frequent in anaemic women (Fareh *et al.*, 2005).

Blood group showed an association with primary PPH (P=0.002). With AB POS as reference, A Rh "D" POS and B Rh 'D" POS, all of which are non-O groups, with an OR of 0.11 and 0.13 respectively were associated with a less risk of primary PPH. This is in line with studies on blood groups and bleeding tendencies. Despite only few studies reporting the relationship of ABO groups with haemorrhagic disorders, older studies have established that VWF levels (associated with haemostsasis) are 25-35 percent lower in subjects with type-O blood than in non-O individuals (Gill *et al.*, 1987). More recent studies have also emphasized this fact (Miller *et al.*, 2003) and the role of VWF in coagulation cannot be overemphasized in its complex formation with FVIII and Ca in the latter stages of the intrinsic pathway. These factors may be attributed to the finding in the current study; therefore the fact that the above non-O group individuals are less prone to bleeding tendencies is still valid.

The ESR was generally elevated amongst all the women under study (median 56mmfall/hr). That of the PPH cases was also higher than that of non-PPH controls. This however was not associated with odds for primary PPH. It has been explained that ESR levels are expected to rise during pregnancy due to the increase in fibrinogen, plasma expansion and anaemia but the upper limit has not been clearly defined (van den Broe and Letsky, 2001). But for highly elevated levels that could be associated with an acute phase response, the elevated levels in pregnacy are generally not expected to be associated with pathology, as seen in the current study. It has been further suggested that a correct interpretation of the ESR must be based on other factors like gestational age and the HGB levels (van den Broe and Letsky, 2001).

An abnormal blood picture from an examined thin blood film of the women was not associated with the likelihood of developing primary PPH (OR=0.16). Therefore, blood film comments to detect abnormalities might not be a significant factor in screening for predictors of the condition. However, we recommend that any abnormalities in blood picture must be accompanied and interpreted with other laboratory tests to establish any bleeding tendencies during delivery. Intepretation must also be in contex of current condition of the patient in question.

5.8 DIAGNOSIS OF PRIMARY PPH: ACCURACY OF BLOOD LOSS ESTIMATION

Ability to determine accurately the blood loss during childbirth is of extreme importance in the diagnosis and management of PPH (Lalonde *et al.*, 2006). It has been suggested that estimation of the exact amount of blood loss is subjective and hence no gold standard method for estimation in most facilities (Lalonde *et al.*,

2006; Ramanathan and Arulkumaran, 2006). This can lead to a gross underestimation of PPH by up to 50% (NSW, 2010).

As with the method employed in the current study, we were able to measure blood loss objectively and were compared to visual estimation of the same. When both methods were compared, the mean blood loss for calibrated measurement was 306 mls opposed to 250 mls in visual estimation with a bias of 56 mls ($P<0.0001$) and an ROC of 0.6104. This indicates an underestimation by the method, making it unsuitable for blood loss estimation. This is in line with other studies that have also proved that visual estimation is unreliable for the diagnosis of primary PPH (Duthie *et al.*, 1991). With visual estimation, only 43 of the total participants in the current study would have been diagnosed as primary PPH. This gives a prevalence rate of 12.35%, an underestimation of about 3.5%. In similar studies where visual estimation was compared with other methods, the prevalence of PPH was 8.9% and 16.2% by visual estimation and with changes in haematocrit respectively (Wangwe and Balandya, 2012), an underestimation by the former. Carroli and colleagues also confirmed this with a reliable systematic review, where in about 19 studies that accurately measured the blood loss, prevalence was found to be 10.5% compared to 7.23% in 22 others, which estimated blood loss by visual examination (Carroli *et al.*, 2008). This adds to evidence that the visual estimation of blood loss in clinical setting is not reliable and can lead to near-miss diagnosis of primary PPH and thus an underestimation of the condition. We therefore recommend that blood losses be measured with other methods as reported in other studies.

Chapter 6

CONCLUSIONS

6.1 CONCLUSION

As the deadline for the MDG's fast approaches, the prevalence of primary PPH among this population remains an issue of public health concern and preventive measures need to be put in place.

Visual estimation of blood loss is inaccurate and has a huge potential to underestimate the occurrence of primary PPH, and perhaps aggravate its associated morbidity and mortality.

Previously hypothesized risk factors for PPH such as age, ethnicity, parity, history of PPH and BMI, which were included in the current study together with additional factors such as AST, ALB, URE, and ESR were not significantly associated with primary PPH.

Increasing CRE, URE/CRE ratio, and decreasing HGB levels among this population were associated with the development of primary PPH. However, non-O blood types (A and B rhesus "D" Positive) groups were associated with a reduced risk of primary PPH development. Therefore though many antenatal clinical and laboratory factors may be associated with primary PPH only a few may have utility for screening and assessment of target groups.

6.2 RECOMMENDATIONS

With the high prevalence rates of primary PPH among women in Ghana, the current urgency with which the condition is handled must be increased in attempts to bring down the numbers.

Health care facilities that continue to practice visual estimation of blood loss in the diagnosis of PPH should adopt other and more accurate methods of blood loss estimation. This will increase chances of diagnosis and help manage and reduce various morbidities and mortality associated with PPH.

Despite the many factors known to be associated with primary PPH, only a few are predictive. Efforts to reduce incidence of primary PPH must not only be directed toward the assessment of previously hypothesized factors and proper management of labour but also on the sensitization of target health care workers to do a total work-up which includes clinical, obstetric and laboratory evaluation. However, preparations should be made as the unexpected may happen.

With limited data, further work must be done in the subject area among the Ghanaian population to establish the importance of laboratory factors in the prediction of primary PPH.

A wider ethnic-based study must also be conducted to establish ethnicity as a risk factor.

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