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Etiology and treatment of postpartum hemorrhage in low- and middle-income countries

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Thesis

**ETIOLOGY AND TREATMENT OF POSTPARTUM HEMORRHAGE IN
LOW- AND MIDDLE-INCOME COUNTRIES**

by

KAYLEE BRESSLER

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Approved by

First Reader

Davidson H. Hamer, MD
Professor of Global Health and Medicine

Second Reader

Nafisa Halim, MA, PhD
Research Assistant Professor, Global Health

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ABSTRACT

Postpartum hemorrhage (PPH) is the leading direct cause of maternal mortality worldwide, with the majority of deaths taking place in the least developed countries of the world. Low- and middle-income countries (LMICs) have increased rates of PPH due to lack of access to healthcare, inadequate number of care providers and availability of interventions and resources needed. PPH has four main etiologies: uterine atony, trauma, retained placenta and coagulopathy. The most common and challenging to treat is uterine atony, where a lack of uterine contractility leads to massive hemorrhage postpartum. Specific risk factors have been identified that increase a woman's risk of developing PPH. Risk factors of PPH can be categorized as biological, demographical and social risk factors. Many people in LMICs experience a lot of the social risk factors like lack of providers, skilled facilities and resources available to them in case of an obstetric emergency. Home births are also a common practice in many LMICs, placing a woman further from any resources she may have had access to if she was at a health facility. PPH can also occur in women without risk factors and requires that providers always be prepared to treat it. Interventions to treat PPH are well known and encompass both pharmacological and non-pharmacological interventions that are usually tried in a least to

most invasive order. The first line of intervention is often to administer a uterotonic drug, preferably oxytocin. This poses a challenge to LMICs because oxytocin requires a cold-chain storage, which many LMICs countries lack. Therefore, uterotonics and non-pharmacologic interventions have increasingly been used in these regions. The final and ultimate life saving measure to stop bleeding is a hysterectomy, which is often not available in these rural places where home births take place, and has led to higher mortality rates. Prevention measures of PPH include increasing antenatal care (ANC) use and practicing active management of the third stage of labor (AMTSL) with all pregnancies. Use of ANC and ultrasound technology can help identify the biological risk factors that make a woman more likely to experience PPH. Solutions to lowering the occurrence of PPH in LMICs involve increasing resources and access to healthcare. An important part to increasing access is increasing the number of skilled health facilities and health providers. Community health workers (CHW) and skilled birth attendants (SBA) are vital to increasing the amount and acceptability of care in these regions. These workers are trusted members of the community that can help educate and bring resources to women, as well as women to the resources. Solutions to stopping PPH need to consider the affordability, acceptability and accessibility in order to reach people in remote areas with limited resources. Both immediate short-term interventions and long-term, longitudinal healthcare reform are necessary to save mothers in LMICs.

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LIST OF ABBREVIATIONS

AIDS	acquired immunodeficiency syndrome
AMTSL	active management of the third stage of labor
ANC	antenatal care
cAMP	cyclic adenosine monophosphate
CHV	community health volunteer
CHW	community health worker
EmONC	emergency obstetric and newborn care
FFP	fresh frozen plasma
GI	gastrointestinal
HIV	human immunodeficiency virus
IM	intramuscular
IV	intravenous
LAC	Latin America and the Caribbean
LMIC	low- and middle-income countries
MMR	maternal mortality ratio
MTP	massive transfusion protocol
NCD	non-communicable disease
PGE	prostaglandins
PPH	postpartum hemorrhage

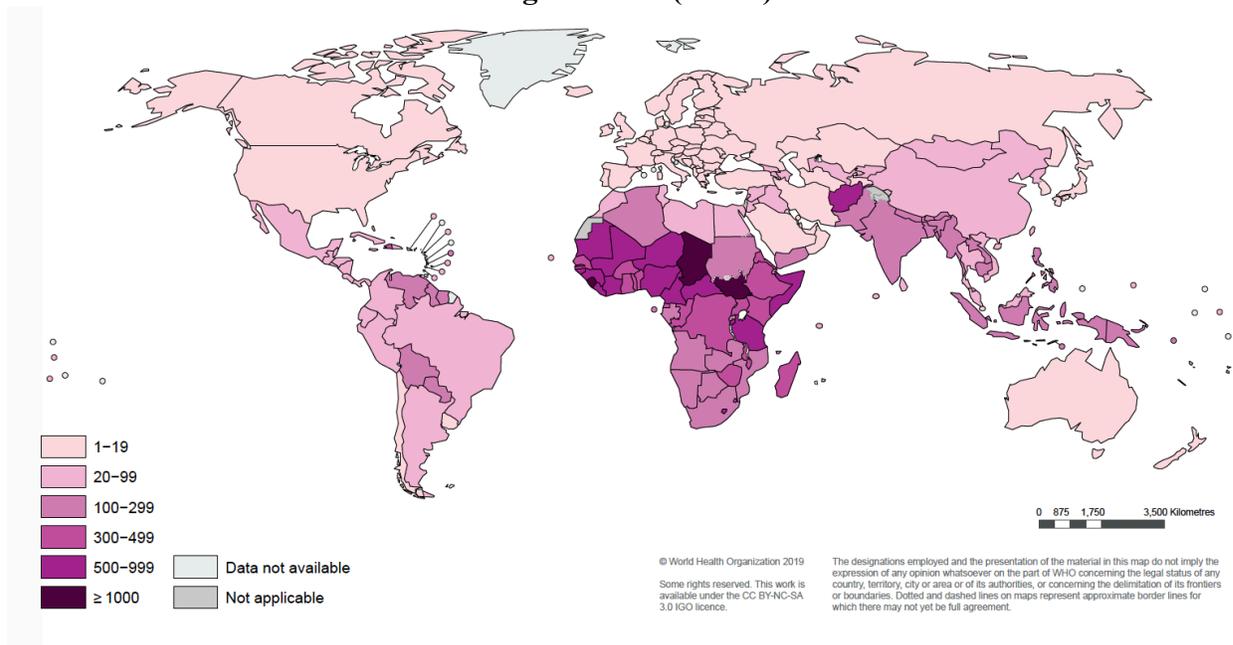
PRBC	packed red blood cells
SBA	skilled birth attendant
SCAH	supracervical hysterectomy
TAH	total hysterectomy
TBA	traditional birth attendant
TTI	time-temperature indicator
TXA	tranexamic acid
UK	United Kingdom
WHO	World Health Organization
WOMAN	world maternal antifibrinolytic

I. INTRODUCTION

Prevalence

In 2017 maternal mortality was estimated at 295,000 deaths worldwide, giving a maternal mortality ratio (MMR) of 211 maternal deaths per 100,000 live births.¹ The MMR estimate of the least developed countries (countries with a gross national income <\$3,995²) was 415 maternal deaths per 100,000 live births, 40 times higher than Europe's MMR.³ This is graphically represented in Figure 1, which shows the MMR in each country. This is a decrease of 38% from 2000, when the estimated MMR was 342 maternal deaths per 100,000 live births.³ The leading direct cause of maternal mortality was reported as postpartum hemorrhage (PPH), representing 27.1% of all deaths.⁴ The treatment of PPH is well known and can include the use of uterotonic drugs, uterine tamponade, blood transfusion and in some cases, surgery.⁵ However, the use of these treatments in low- and middle-income countries (LMICs) is reduced due to lack of access and limited resources, making both prevention and treatment more difficult.

Figure 1: 2017 Maternal mortality ratio (MMR), deaths per 100,000 live births. Taken from the World Health Organization (WHO)¹



Objectives

The goal of this thesis is to review the known etiologies, risk factors and interventions used for PPH, while looking at them in the context of a resource limited setting, in order to identify the best strategies to implement in order to lower the occurrence of PPH in LMICs. First, the four etiologies of PPH will be identified, taking into consideration the physiological changes that occur in a woman during pregnancy. Second, biological, demographical and social risk factors that increase the incidence of PPH will be identified. Then interventions, both pharmacological and non-pharmacological, will be discussed in context to them being used in a resource limited setting. Lastly, the best prevention strategies for LMICs, and how they can be

implemented in the future will be given. Concluding with the best strategies to be implemented in resource limited settings to decrease the occurrence of PPH.

II. POSTPARTUM HEMORRHAGE

Definition

Postpartum hemorrhage has been defined since the 1990s as the loss of >500 ml of blood after vaginal delivery and loss of >1000 ml of blood after a cesarean section.⁶ However, physicians have been in search of a better definition to more quickly recognize the signs of PPH. The amount of blood loss that will cause clinical consequences is highly variable for each mother and is often a reflection of the mother's health. In addition to this variability, the measurement of the amount of blood lost is unreliable because the current standard is visual estimation, which underestimates the true amount by 33-50%.⁶ These challenges in measuring blood loss may cause a delay in the diagnosis and treatment of PPH.

A better definition that has been suggested is any amount of blood loss that causes hemodynamic instability. Signs of hemodynamic instability include changes in heart rate, blood pressure, respiratory rate and speed of blood flow.⁶ The major limitation of relying on vital signs for diagnosis is the time lag. By the time a patient's vitals change, a large amount of blood has already been lost, limiting the use of preventative measures and leading to late identification of PPH. The diagnosis of PPH is still a highly clinical decision and gives the physician freedom to manage individual patients differently,

independent of the amount of blood lost. Finding one cohesive definition is difficult because each pregnancy is different with multiple variables to consider.

Etiology

There are four main causes of PPH: uterine atony, trauma, retained placenta and coagulopathy. Of these, uterine atony is the most common, occurring in 75-90% of PPH cases globally and is often due to overdistension and fatigue of the uterus.⁷ Failure of the uterus to contract leads to massive hemorrhage from the uterus. Trauma to the uterus can result from lacerations, uterine rupture or episiotomy and makes up 20% of PPH cases.⁷ Delivery using instruments can increase the risk of trauma and developing PPH.⁸ In the case of a retained placenta, it creates a physical block and prevents the uterus from contracting, leading to uterine atony and PPH. The least common cause of PPH is from clotting abnormalities, inherited and acquired, which make up 3% of cases seen.⁷ Lack of clotting factors decreases the ability of a clot to form and hold in the uterus, even if the uterus is able to contract. Blood and platelet transfusions are needed to help the blood clot and replace the lost blood.

To understand what happens in PPH and how it is treated, it is important to recognize the physiological changes that occur during pregnancy. The maternal blood volume expands by 40-50%, in part to protect against hemorrhage.⁷ A woman may lose 20% of her total blood volume before any clinical signs are seen. At term the blood flow to the uterus is between 800-1000 ml/min, allowing blood loss to occur readily.⁷ The amount of blood loss is dependent on the contraction and retraction of the interlacing

myometrial fibers of the uterus that surround the placental spiral arteries. Failure of the uterus to contract will result in massive hemorrhage, namely postpartum hemorrhage.

The contraction of the uterus is a mechanical event that is mediated by hormones and occurs throughout labor to facilitate delivery of the child and the placenta. The delivery of the placenta occurs during the third stage of labor and begins after delivery of the child. It is often termed afterbirth and consists of two phases: contraction and detachment.⁹ The contraction phase consists of the placental site of the uterine wall undergoing thickening. Then in the detachment phase the placenta completes its separation from the uterus and is delivered. Contraction of the uterus is largely dependent on hormone signals, specifically oxytocin.

Oxytocin is the main hormone that binds to receptors and increases the uterine contractility. There is a proliferation of oxytocin receptors on the myometrium throughout pregnancy and during labor.⁹ Oxytocin is released in a pulsatile manner from the posterior pituitary, with the frequency and duration of release both increasing during labor. Prostaglandins (PGE) also act to increase uterine contractility during labor, specifically PGE₂ and PGF₂ α . They act via cyclic adenosine monophosphate (cAMP) mediated calcium release to increase calcium concentration and muscle contraction.⁹ They are produced locally by the decidual tissue, placental tissue and the fetal tissue. The plasma concentration of clotting factors also increases during labor to help clot the blood once the placenta detaches, helping to limit blood loss.

When the body's mechanisms fail to elicit uterine contraction, as in uterine atony, the uterus requires additional stimulation to make it contract. Treatment of PPH is

focused on utilizing the body's same mechanisms of action to trigger uterus contraction. Synthetic oxytocin and other drugs with a similar mechanism of action have been developed to increase uterine contractility. Physical interventions have also proved useful to stimulate uterine contractions. These interventions can be used for both prevention and treatment of PPH if diagnosed early enough. Early recognition is key to treating PPH, making it important to know the risk factors and warning signs of PPH.

Risk Factors

The main risk factors for PPH can be divided into three categories: biological, demographical and social risk factors.¹⁰ A lot of research has been done on biological risk factors in high-income countries, which can be applied universally since all women's physiology works relatively the same. One of the most common biological risk factors is overdistension of the uterus which is seen in polyhydramnios, multi-fetal gestations and fetal macrosomia.¹¹ Over distension of the uterus can make it harder for the uterus to contract, leading to uterine atony. This can be diagnosed with prenatal ultrasound screenings and allow a birth plan to be put in place. Any woman who has a history of PPH is also at an increased risk of PPH reoccurring.¹²

The progression of labor, either too fast or too slow, can also be a risk factor for uterine atony. If labor proceeds rapidly, the rigorous contractions during child birth tire the uterus out leading to atony. In addition, prolonged labor will also tire the uterus out from working so hard, and the contractions will not be forceful enough to constrict the spiral arteries to prevent hemorrhage.⁸ Induced and augmented labor have also been

shown to increase the risk of PPH. Both of these situations involve using oxytocin to trigger uterine contractions to start and speed up labor, respectively. A study done by Mansy (2017) showed a greater amount of blood loss in patients who had augmented labor with oxytocin than those who had no augmentation of labor.¹³ Due to the increased risk of PPH, augmentation of labor is only recommended when there is abnormal fetal presentation, inadequate bony pelvis of the mother, or inefficient uterine contractions.

More chronic, prenatal causes of PPH are pre-eclampsia, noncommunicable diseases (NCD), and infection. Pre-eclampsia is a serious medical condition most commonly presenting as hypertension and proteinuria, but can encompass many other physiological symptoms.¹⁴ The diagnosis of pre-eclampsia during pregnancy allows for it to be monitored, managed, and PPH prevention measures to be taken. Women with pre-eclampsia should give birth in a healthcare facility to allow for greater access to resources if needed. The women should then be educated on postnatal care, and the necessary healthcare she may need in the future.

Noncommunicable diseases such as obesity, diabetes, undernutrition, and hypertension can lead to more adverse events during pregnancy and the time of fetal programming.¹⁵ The impact of intrauterine programming has effects on later life events, like the risk of NCD development. This link between maternal health, child health, and NCDs gives incentive to integrate these health services to stop the perpetuation of this cycle of poor health from mother to child. High blood pressure and high blood sugar are two of the leading risk factors for maternal mortality. Many of these biological risk factors can be diagnosed during the prenatal period by use of screenings. Making primary healthcare

more accessible is necessary to treat NCDs, reduce the maternal mortality rate, and increase children's health, all at the same time.

Demographic risk factors have been evaluated in several studies in high-income countries and in LMICs. The greatest risk factors for PPH include maternal age, education level, ethnic group, and marital status. Maternal age was a significant indicator of PPH with higher maternal age, greater than 35, having an increased occurrence.¹⁶ Education level was not a direct indicator of PPH but was associated with prolonged labor and the number of skilled providers present, which are associated with a high risk of PPH¹⁰. Studies looking at race have found an increase in the risk of severe morbidity from PPH in non-Hispanic black women.¹⁷ These findings are in line with the overall maternal mortality risk for non-Hispanic black women, which is 3.5 times more than other women. The fact that non-Hispanic blacks are at higher risk, paired with a lack of resources to prevent and treat complications, has led to the increased maternal mortality that has been seen in sub-Saharan Africa. This region suffers from the highest maternal mortality ratio of 533 maternal deaths per 100,000 live births.¹⁸

Social barriers to obstetric care include the geographical location of facilities, lack of skilled providers, resources available, cultural factors, and socioeconomic status. All of these barriers prevent people from having access to healthcare facilities. The main components of access can be divided into three categories; availability, affordability, and acceptability.¹⁹ All three must be considered when trying to help bring care to people in other countries. Increasing resources, facilities, and providers are a part of the availability of healthcare. Skilled healthcare facilities should be equipped to provide signal functions

for emergency obstetric and newborn care (EmONC).²⁰ These facilities have the resources and providers to provide several life-saving obstetric interventions in emergencies. The United Nations has defined nine key services: administration of parenteral antibiotics, uterotonics, anticonvulsants for pre-eclampsia and eclampsia, manual removal of the placenta, retained products, assisted vaginal delivery, basic neonatal resuscitation, performance of caesarean sections and blood transfusions.²¹ These indicators are used to provide a standard of care that facilities should be able to provide to women in case of obstetric emergencies.

The minimum acceptability level of availability is 5 EmONC care facilities for every 500,000 population.²¹ This takes into consideration the geographical distribution of the facilities, how accessible they are, and the modes of transportation people have access to.²² With limited roadways and uses of transportation, getting to a facility can be difficult and nearly impossible for people in remote villages. Looking at ways to expand infrastructure and roadways is a part of increasing availability of healthcare to people no matter where they live.

Affordability may be the most important aspect to consider but may take the most work to reform. If there are facilities and people to provide care but no one to pay for that care, it is not a very successful healthcare system. As the name implies, LMICs have a large population of people below the poverty line. Often times an injury or diagnosis can drive a family into poverty. If someone is sick, they cannot go to work, and if they can't work, they have no income. Working to put an affordable and useable healthcare system in place is necessary to allow people to use healthcare and not end up in poverty. This

will require political leaders, policy writers, and providers working together to create a cohesive plan. These plans are unique to each individual country and the unique needs of the people they serve.¹⁹

Lastly acceptability of services depends on the cultural and social practices of a community. This includes variables such as community and cultural preferences, the households' expectations, a woman's assertiveness, and the amount of stigma and health awareness.¹⁹ There is a need for more culturally competent healthcare systems and providers to improve acceptability. Common community and cultural preferences include home births, having family members present, and unwillingness to see a male provider.¹⁹ A woman's lack of assertiveness can result in the need for her husband's permission, his denial of permission, and delayed decision making. In addition, the lack of perceived need and stigmas associated with HIV-pregnancies have been obstacles to seeking proper care.¹⁹ The goal of cultural competency is to reduce the racial and ethnic health disparities that are commonly seen in healthcare services.²³ Each community will require a different strategy in order to take their cultural components into consideration while working to increase healthcare services to women. All three components of access are necessary to increase the use of healthcare, wherever it may be implemented.

Being aware of these risk factors for PPH can lead to better prevention and increased preparedness for birth. Education and training of providers is necessary so they know these factors and can identify women at risk. They can then also educate the women and their families on any precautions that should be taken. It is important to note that PPH can happen in woman with no risk factors, so it is crucial to always be prepared.

II. INTERVENTIONS

Interventions for PPH can be classified into two main groups: pharmacological and non-pharmacological interventions. The course of treatment chosen is largely up to the physician but often proceeds from least invasive to most invasive. The type of intervention also depends on the etiology and severity of PPH. Traditionally, early recognition of PPH due to uterine atony is first treated with uterine massage followed by use of a uterotonic agent. If those fail to stop the bleeding more invasive non-pharmacological treatments will be used. Moving into the later stages of PPH, when a life-threatening amount of blood has been lost, surgical intervention may be necessary to save the mother's life. The interventions listed below will be based on PPH due to uterine atony. These treatments are well known and accessible in high-income countries but using them in LMICs comes with more challenges, making some of them ineffective.

Pharmacological Interventions

Table 1. Comparison of uterotonic agents used to treat PPH.

<i>Intervention</i>	<i>What it is</i>	<i>Advantages</i>	<i>Limitations</i>	<i>When it is best to use</i>	<i>Cost effectiveness²⁴</i>
Oxytocin	Synthetic oxytocin peptide	Favorable side effects profile, fast acting	Need skilled provider for injection (IV or IM), requires protection from light and cold chain storage	When it is kept in proper storage conditions and a skilled provider is present to give injection	US \$1.18 Lifesaving and cost-effective

Carbetocin	Synthetic agonist analogue of oxytocin	Favorable side effects profile, heat stable formulation available	Need skilled provider for injection (IV or IM), higher cost	When a skilled provider is present	US \$23.11 WHO is in talks with manufacturer to make it similarly priced to oxytocin for countries in need
Misoprostol	Synthetic analogue of PGE1	Administered via sublingual, oral, vaginal or rectal (no skilled provider needed), no special storage requirements	Increased side effects (GI problems; nausea, vomiting, diarrhea and abdominal pain)	When no other uterotonic agents are available, when there is no skilled provider present	US \$0.66 Cheaper than oxytocin, may be good option for LMICs that have low rates of skilled attendant births
Ergometrine	Ergot alkaloid	Increases effectiveness of oxytocin when given in combination, increased vasoconstriction effects	Contraindication of hypertension, increased adverse effects (hypertension, pain, nausea and vomiting), need skilled provider for administration (IV)	If oxytocin alone was not effective, may give in combination with additional oxytocin dose	US \$1.97 If available to give in combination with oxytocin may have increased effect
Tranexamic acid	Antifibrinolytic agent	Enhances body's own clotting mechanisms	Need skilled provider for administration (IV), more research needed on optimal dose	When all other uterotonic options have been exhausted	US \$0.0378 ²⁵ Routine use of TXA in obstetric hemorrhage is cost effective in the US, need additional research evaluate effectiveness in LMICs

A. Oxytocin

The number one choice of uterotonics is synthetic oxytocin. It is a synthetic peptide hormone that mimics the effects of endogenous oxytocin released from the posterior pituitary. The hormone binds to oxytocin receptors on the myometrium and increases the

sodium permeability of the myofibrils, leading to increased uterine contractility.²⁶ The contraction of the myometrium constricts the spiral arteries of the uterus, decreasing blood flow to the uterus and preventing massive hemorrhage. Oxytocin is an effective first line of treatment and is often used for prevention of PPH, being administered during the third stage of labor.²⁷ There are few contraindications for using the drug and minimal side effects have been reported with short term use. Longer term use with infusion carries the risk for water intoxication and the patient must be monitored closely. While oxytocin seems like the best and most logical choice of drug, it faces a few difficulties when being used in LMICs.

For oxytocin to have effects on the uterus it must be administered intravenously or intramuscularly. Intravenous (IV) infusion works the most rapidly with almost an immediate onset of effects, namely uterine contraction. Intramuscular (IM) injection works more slowly taking 3-7 minutes to produce effects, but has the advantage of having longer lasting clinical effects.²⁶ A study done by Charles et al. (2019) showed that IV administration of oxytocin was more effective than intramuscular injection in preventing PPH.²⁸ Both of these injection methods of oxytocin require a skilled health care provider to be present at the birth, which happens at low percentages in LMICs. This makes oxytocin less accessible for treatment of PPH in LMICs. Without a skilled birth attendant present it is not recommended to use oxytocin.

In an effort to make administration of oxytocin simpler and more accessible in-home settings, PATH has created a device called Uniject™, shown in Figure 2.²⁹ It is a one-time use disposable device that provides a premeasured dose of oxytocin that is

administered intramuscularly to the patient. The goal is to make the delivery of oxytocin easier, safer and more cost effective in order to increase the accessibility and use of oxytocin in prevention and management of PPH. This device has many advantages to the traditional administration of oxytocin. Packaging the dose in an easy to use device eliminates the need for disposable needles, syringes, and the use of ampoules of the drug. This simplifies the steps of delivery of the drug, making it available to health care workers who do not normally give injections. With it being a one-time use device, it also eliminates needles being reused for multiple patients, minimizing the risk of patient-to-patient transmission of bloodborne pathogens.

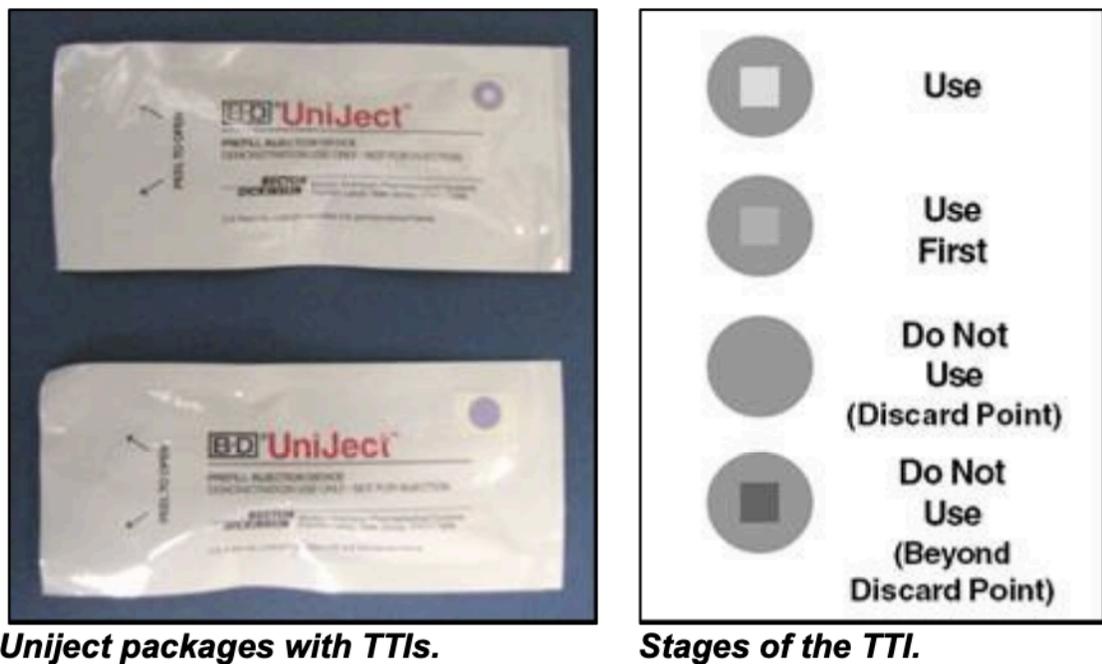
Figure 2. Uniject™ device. A premeasured, single dose of medication in a disposable, easy injectable device. Example shown for a tetanus vaccine. Taken from PATH device overview²⁹



The device comes in a small package that includes a time-temperature indicator (TTI) as shown in figure three. This is important because oxytocin is a heat-labile protein that requires protection from heat and light to keep the active form of the drug intact.³⁰ This label shows the exposure of that package to heat and gives a quick indication of if that dose of oxytocin should be used, or if it needs to be disposed of. When the inner square is

the same color or darker than the outer circle the device should not be used. When that is the case, there has been a significant amount of heat exposure to the drug that has decreased the amount of the active ingredient in the device. Administering the oxytocin at that point would not give the desired clinical effects.

Figure 3. TTI indicator on label. The time-temperature indicator is on the Uniject™ packaging label and reacts to heat exposure. The different symbols show when it is useable and when it needs to be discarded. Taken from PATH device overview²⁹



Tsu et al. (2009), determined whether the Uniject™ device made delivery of oxytocin easier. A survey was given to midwives who used the device to see if it was better than the traditional administration of oxytocin. Researchers reported that the majority of midwives found it easier to use, and preferred it over the use of syringes and ampoules.³¹ One reason cited was the time and effort it took to use syringes and ampoules. Oxytocin is most effective when delivered within two minutes after birth of the baby. Fast

deliveries can lead to rushing to get the syringes and opening the glass ampoules. There is also a chance of injury when opening the ampoules. The glass can potentially cut the hand of the person opening it, slowing down the administration even more. The administration of oxytocin using the Uniject™ device eliminated risk of injury and the extra time spent getting the injection ready seen in traditional administration.

In another study by Pichon-Riviere (2015), the cost-effectiveness of the Uniject™ device was looked at versus the traditional administration of oxytocin in Latin America and the Caribbean (LAC). They found that using the Uniject device could prevent 40,000 cases of PPH annually in LAC. The device was found to increase health and reduce health care costs of PPH in 30 countries.³² While more studies are needed to know if the Uniject™ device will increase utilization of oxytocin, these are promising results for making oxytocin more accessible to LMICs.

As touched on previously, the other challenge of using oxytocin in LMICs is its storage requirements. It is recommended to store oxytocin at a temperature of 2-8°C.²⁶ Changes in the physical and chemical environment can change the drug's structure, rendering it inactive and ineffective. In LMICs there is not consistent and reliable access to cold storage and the active dose often drops to levels below the effective dose that is needed. This challenge is common in LMICs and has been seen with other heat-sensitive materials, like vaccines. Solutions that have been proposed have included innovative packing and storage coolers, and the creation of heat stable formulations. Scientists have been in search of a heat stable oxytocin formulation that can be administered without use of injection to make it more accessible to developing nations.

One study attempted to alleviate both of these challenges by creating a heat stable sublingual oxytocin tablet, allowing it to be used without cold storage or skilled birth attendants. Using a freeze-drying technique, they were able to create a fast-dissolving tablet that maintains stability up to temperatures of 40°C, and at a relative humidity of 75%.³³ This pharmacokinetic study was done in pigs and demonstrated that the sublingual route resulted in increased plasma levels of oxytocin. Whether this route of administration will provide therapeutically effective levels in humans is yet to be studied. While efforts to make oxytocin more stable and accessible in developing countries are in development, there are multiple other uterotonic drugs that have been recommended for use in the absence of oxytocin.

B. Carbetocin

Carbetocin is a synthetic oxytocin agonist that elicits the same response as oxytocin, stimulating consistent and rhythmic contractions of the uterus. It is also similar to oxytocin in its limited side effects profile and route of administration, being administered via IV or IM injection.²⁶ The most favorable difference between oxytocin and carbetocin is that a heat-stable version of carbetocin has been synthesized, making it a much better drug to use in the hot climates of LMICs.³⁴ Although a skilled health care provider would still be needed to give the injection, the need for a cold chain for transport and storage would be eliminated. The one drawback to carbetocin is that it is almost twenty times the cost of oxytocin, making it less attractive for use in LMICs.

Recently, the WHO has added the use of carbetocin to its recommendations for treating PPH. This came after a study that proved heat-stable carbetocin was non-inferior to oxytocin at preventing blood loss of greater than 500 mL.³⁵ The high cost of the drug is being overcome by the WHO signing a memorandum of understanding with the pharmaceutical company that produces carbetocin.³⁶ This agreement would make carbetocin available to LMICs at a price similar to that of oxytocin. Carbetocin is currently in the process of being registered in many LMICs to make this heat stable uterotonic drug more available for use.

C. Misoprostol

Misoprostol is a prostaglandin E1 analogue that is often used as a second, or third line agent for PPH. It works by binding to receptors on the myometrium to increase intracellular calcium levels, leading to strong uterine contractions.³⁷ Misoprostol has been recommended for use in LMICs due to its heat stability and easy administration.³⁸ It is available as a tablet that can be administered as an oral, sublingual, vaginal, or rectal dose. For treatment of PPH, the most effective in stimulating uterine contractions is the oral and sublingual routes.²⁶ They work the fastest and give the highest plasma concentration of misoprostol acid, the active compound. The biggest disadvantage to using misoprostol and prostaglandin agonists in general, is the high rate of side effects.

Prostaglandins are found in many different parts of the body, a major one being the gastrointestinal (GI) tract. Misoprostol was originally marketed for the treatment of peptic and duodenal ulcers. Using misoprostol to treat PPH comes with a high occurrence

of GI problems including nausea, vomiting, diarrhea, abdominal pain, fever, and chills.³⁷ Although unpleasant, these side effects are not life threatening. Which is why it is still considered for the management of PPH, especially in low income countries where injectable uterotonics are not available.

Another consideration with the use of misoprostol is the potential for it to be misused at earlier stages in the pregnancy. When given during the first trimester or the early part of the second trimester of pregnancy, it can induce abortion of the fetus. While it is normally given in combination with mifepristone or methotrexate for medical abortions, use of misoprostol alone has resulted in successful abortions.³⁹ The administration and use of misoprostol must be monitored to make sure it is being used for treatment of PPH and not abortions.

D. Ergometrine

Ergometrine is an ergot alkaloid that stimulates the uterus to contract through a non-specific receptor mechanism.²⁶ It is most commonly given in combination with oxytocin in a measured dose. Ergometrine has increased vasoconstriction action, thought to make oxytocin more effective.⁴⁰ However, this also increases the number of adverse effects observed. Side effects most commonly seen are hypertension, pain after birth, nausea, and vomiting. It is not recommended to use in patients with a pre-existing condition of hypertension, a symptom often seen in cases of pre-eclampsia.

The use of combination ergometrine and oxytocin continues to be used despite studies that say it offers no significant clinical advantage to oxytocin alone.⁴¹ Oxytocin is even

seen as favored over the combination dose because of fewer adverse effects. A study done by Van der Nelson et al. referenced an unpublished phone survey of obstetric units. These units reported that they had noticed increased rates of PPH in their audits when using just oxytocin.⁴⁰ The units then decided to revert to the ergometrine/oxytocin combination drug. Although no studies have found a significant difference in rates of PPH between the drugs, what people experience and perceive has had an impact on what interventions are used.

E. Tranexamic Acid

Tranexamic acid (TXA) is an antifibrinolytic agent that slows the breakdown of blood clots to prevent bleeding. It specifically blocks lysine binding spots on plasminogen, a protease that is involved in breaking down fibrin blood clots.⁴² Administration of TXA is via IV infusion, and has the ability to enhance the body's own clotting mechanisms to reduce bleeding. TXA has been proven to work in other situations such as post-operative patients, trauma patients and during menstrual blood loss.⁴³ However, the current studies that have been done on its use for PPH are insufficient to make the recommendation of widespread use for prevention and treatment of PPH.

The WHO saw the need for more studies, and the WOMAN (world maternal antifibrinolytic) trial was conceived as a research study. The study evaluated if TXA could reduce mortality seen from PPH, and if its use increased thromboembolic events in the mother and their breastfed babies. All healthcare settings were represented in the data with Nigeria, Pakistan, Uganda and the UK becoming some of the biggest recruiters for

the trial. The study found that TXA significantly reduced women's risk of bleeding to death and no difference in the number of thromboembolic events between the two groups.⁴⁴ Additional research is needed to answer the remaining questions concerning the optimal dose, route of administration, and its use as a prophylactic drug.

F. Fluid replacement considerations

With a patient losing any amount of blood, there is always consideration of fluid replacement in order to keep the patient hemodynamically stable. In PPH it is first recommended to use crystalloid fluids at the onset of a large amount of bleeding.⁴⁵ Administration of crystalloid fluids helps to reestablish fluid balance by increasing the total blood volume. However, if bleeding continues it may counterproductively hinder the treatment of PPH. The increased blood volume simultaneously causes hemodilution, decreasing the oxygen-carrying capacity and effectiveness of clotting factors. In any case, it is important to keep track of the amount of fluids going in, along with the patient's urine output. Giving too much fluid can also cause adverse effects due to volume overload, such as peripheral edema, shortness of breath and hypertension.

If bleeding continues to the amount of 1500-2000 mL of blood, it is defined as severe postpartum hemorrhage and blood products are then needed for infusion.⁴⁵ Measurement of blood loss is often inaccurate and unreliable, so hypovolemic shock is a sign that blood replacement is needed. A standardized massive transfusion protocol (MTP) has been implemented more regularly in obstetrics when faced with severe PPH. This protocol has a stepwise response to massive blood loss that allows for all the team members to be on

the same page, to act fast, go through each step in order and limit errors.⁴⁵ Activation of an MTP results in transfusion of packed red blood cells (PRBC), fresh frozen plasma (FFP), platelets and recombinant factor VIIa. This will increase the blood carrying capacity, blood volume and the clotting ability.

In community settings where women give birth in a place other than a hospital, fluid replacement is not possible. Even in a hospital, there may not be access to blood products for administration to the patient. So even if the bleeding can be treated and stopped, without replacement of fluid the woman may still die from hypovolemic shock. The only real way to fix this problem is by increasing women's access to healthcare facilities. This is why there is a large emphasis on prevention, early detection and early intervention of PPH. As a woman develops severe PPH, there are even fewer resources available to ensure her health and survival.

Cost effectiveness

It is important to consider the cost of these uterotonics when trying to implement them into regions with a high rate of poverty. A study done in the UK looking at the cost effectiveness of uterotonic drugs for prevention of PPH found that oxytocin, carbetocin and ergometrine/oxytocin were the most cost effective.⁴⁶ They mention that if carbetocin's price was reduced it may be the most favored uterotonic, with its high effectiveness and low rates of adverse events. The study gave a good initial look but more evidence is needed to give good reason to change what the choice uterotonic is. In

addition, the paper mentions creating a model that can be adapted to LMICs where PPH occurrence is much higher.

A study done by Lawrie et al. took on this task by evaluating the cost effectiveness of uterotonics in relation to LMICs. They more seriously looked at misoprostol because of its oral administration and no specific storage requirements making it more accessible in remote regions. Misoprostol was found to be cost effective compared to use of no uterotonic in community settings where no skilled birth attendant present.²⁴ The uterotonic was often given by a lay health care worker, and in one study was given to women prenatally to be self-administered during birth. Giving misoprostol to women to self-administer needs to be carefully considered and monitored with the chance of it being misused for medical abortions. Table 1 shows their findings and compares the uterotonics based on cost, desirable effects, risk of adverse effects and resources needed. There is no one drug that meets all the criteria to be the perfect drug to use, one aspect must be compromised. With misoprostol the increased risk of adverse side effects is that compromise. These side effects are not life threatening, making it a powerful choice to prevent mortality from PPH. More studies are still needed, as these findings were reported with uncertainties due to methodological limitations and poor quality of reporting, a common occurrence in data taken from developing countries.

Table 2. Cost effectiveness of select uterotonic drugs. Comparison of the top uterotonic choices by cost, desired effects, risk of adverse effects and resources needed. Table taken from Lawrie et al. 2019²⁴

	Oxytocin (10 IU)	Carbetocin (100 µg)	Misoprostol (600 µg)	Injectable prosta-glandin: Carboprost (250 µg)	Ergometrine (500 µg)	Oxytocin (5 IU) plus ergometrine (500 µg)	Misoprostol (400 µg) plus oxytocin (10 IU)
Indicative uterotonic agent costs²²							
£	0.90	17.64	0.50	18.20	1.50	1.51	1.22
US \$ ^c	1.18	23.11 ^d	0.66	23.84	1.97	1.98	1.60
Relative cost compared with oxytocin (10 IU) ^e	1	19.60 ^f	0.56	20.22	1.67	1.68	1.36
Relative risks of desirable effects (in terms of reduction)							
PPH ≥1000 mL	1	0.87 (0.62–1.21)	1.19 (1.01–1.42)	0.88 (0.41–1.89)	0.94 (0.48–1.84)	0.83 (0.66–1.03)	0.88 (0.70–1.11)
Blood transfusion	1	0.81 (0.49–1.32)	0.88 (0.68–1.13)	0.66 (0.25–1.72)	1.11 (0.54–2.28)	0.78 (0.59–1.03)	0.52 (0.38–0.70)
Additional uterotonics	1	0.45 (0.34–0.59)	1.04 (0.88–1.24)	0.55 (0.31–0.96)	0.97 (0.69–1.36)	0.66 (0.51–0.85)	0.57 (0.44–0.74)
PPH ≥500 mL	1	0.72 (0.56–0.93)	1.08 (0.97–1.22)	1.05 (0.73–1.51)	1.09 (0.85–1.39)	0.70 (0.59–0.84)	0.70 (0.58–0.86)
Maternal death	1	2.00 (0.37–10.92)	0.62 (0.14–2.74)	No estimate	No estimate	No estimate	No estimate
ICU admissions	1	1.16 (0.67–2.02)	1.16 (0.55–2.43)	No estimate	0.39 (0.01–10.27)	2.99 (0.12–73.32)	0.50 (0.05–5.47)
Relative risks of undesirable effects							
Shivering	1	0.77 (0.46–1.29)	4.18 (3.34–5.23)	0.50 (0.19–1.31)	1.31 (0.86–1.99)	1.38 (0.86–2.22)	3.62 (2.59–5.05)
Fever	1	1.07 (0.43–2.69)	3.87 (2.90–5.16)	1.12 (0.33–3.86)	0.77 (0.44–1.35)	0.70 (0.35–1.42)	3.14 (2.20–4.49)
Nausea	1	1.00 (0.71–1.41)	1.42 (1.10–1.81)	2.25 (1.16–4.39)	2.40 (1.65–3.49)	2.03 (1.47–2.79)	1.88 (1.14–3.09)
Vomiting	1	0.93 (0.64–1.35)	1.63 (1.25–2.14)	3.76 (1.90–7.41)	2.36 (1.56–3.55)	2.93 (2.08–4.13)	2.11 (1.39–3.18)
Diarrhea	1	No estimate	2.24 (1.64–3.05)	23.41 (11.03–49.7)	2.51 (1.20–5.26)	1.80 (1.18–2.75)	1.82 (1.12–2.98)
Hypertension	1	1.24 (0.28–5.56)	1.50 (0.49–4.61)	1.40 (0.09–20.66)	8.54 (2.12–34.48)	2.48 (0.89–6.88)	No estimate
Abdominal pain	1	1.13 (0.90–1.44)	1.02 (0.80–1.31)	1.41 (0.39–5.09)	2.13 (0.98–4.62)	1.39 (0.91–2.13)	1.93 (0.89–4.20)
Headache	1	0.94 (0.66–1.33)	0.98 (0.69–1.40)	1.76 (0.33–9.31)	1.89 (1.02–3.50)	1.08 (0.73–1.61)	1.48 (0.42–5.81)
Other resource requirements relative to oxytocin							
Staff and training	Trained maternity staff ^g	Same as for oxytocin	Trained lay health workers can also administer	Same as for oxytocin	Same as for oxytocin	Same as for oxytocin	Same as for oxytocin ^h
Supplies	Needle, syringe, and swab US \$0.07 ²⁸	Same as for oxytocin	No needle, syringe and swab needed	Same as for oxytocin	Same as for oxytocin	Same as for oxytocin	Same as for oxytocin
Equipment and infrastructure	Cold chain storage ^{h19} ; hazardous waste disposal	Heat stable; also requires hazardous waste disposal	Heat stable	Same as for oxytocin	Same as for oxytocin	Same as for oxytocin	Same as for oxytocin
Staff time	2 min to administer ³³ ; time needed for managing adverse effects is minimal	Same as for oxytocin	Less time to administer, but possibly more staff time managing adverse effects	Possibly more staff time to manage adverse effects	More staff time to manage adverse effects	Possibly more staff time to manage adverse effects	Same as for oxytocin
Supervision and monitoring	Cold chain requires monitoring of stock quality	Possibly more staff time (if not used previously)	Possibly more staff time to manage adverse effects	Possibly more staff time to manage adverse effects	More staff time to manage adverse effects	Possibly more staff time to manage adverse effects	Possibly more staff time to manage adverse effects

Non-pharmacological Interventions

When uterotonics fail to stimulate the uterus to contract it is necessary to consider more invasive and mechanical interventions. These interventions are focused on stimulating the uterus to contract or working to decrease the amount of blood that is going to the uterus. Many of these interventions require a hospital setting with skilled health care professionals, limiting their usefulness in LMICs. With more invasive procedures, it is important to consider the woman's future fertility as an outcome to any procedure done. The order of interventions should go from least to most intrusive but in times of crisis some can be skipped, going straight to a full hysterectomy. This takes away a woman's right to carry more children of her own and should only be considered when all other measures have failed.

A. Uterine massage

Uterine massage is the least invasive non-pharmacological intervention and is often a step in the active management of the third stage of labor (AMTSL).⁴⁷ Massaging the uterus by applying pressure to the lower abdomen after the delivery of the placenta can promote contraction of the uterus.⁴⁸ Uterine massage versus no uterine massage during AMTSL has not been proven to significantly decrease rates of PPH. Since uterine massage is noninvasive and does not have any adverse effects, it is still practiced during AMTSL. There is no harm in using it and there may be a slight increase that the uterus will contract.

B. Bimanual uterine compression

Use of bimanual uterine compression involves placing a fist inside the uterus while simultaneously applying pressure on the uterus from the outside on the lower abdomen.⁴⁹ Compressing the uterus from the inside and the outside puts pressure directly on the blood vessels that are causing the hemorrhage, working to directly stop the bleeding. Although highly effective this procedure is painful for the mother and tiresome for the birth attendant. Compression is needed for at least 5-10 minutes and can last up to 30-60 minutes. In addition, a study done by Harvey et al. evaluated how effective the birth attendants were at correctly performing bimanual uterine compression. They found that only 22% of the attendants were able to correctly perform the compression maneuver, and their total knowledge of PPH management was averaged at 63% .⁵⁰ The effectiveness of this procedure relies directly on the ability of it to be performed correctly by the skilled attendants present at birth.

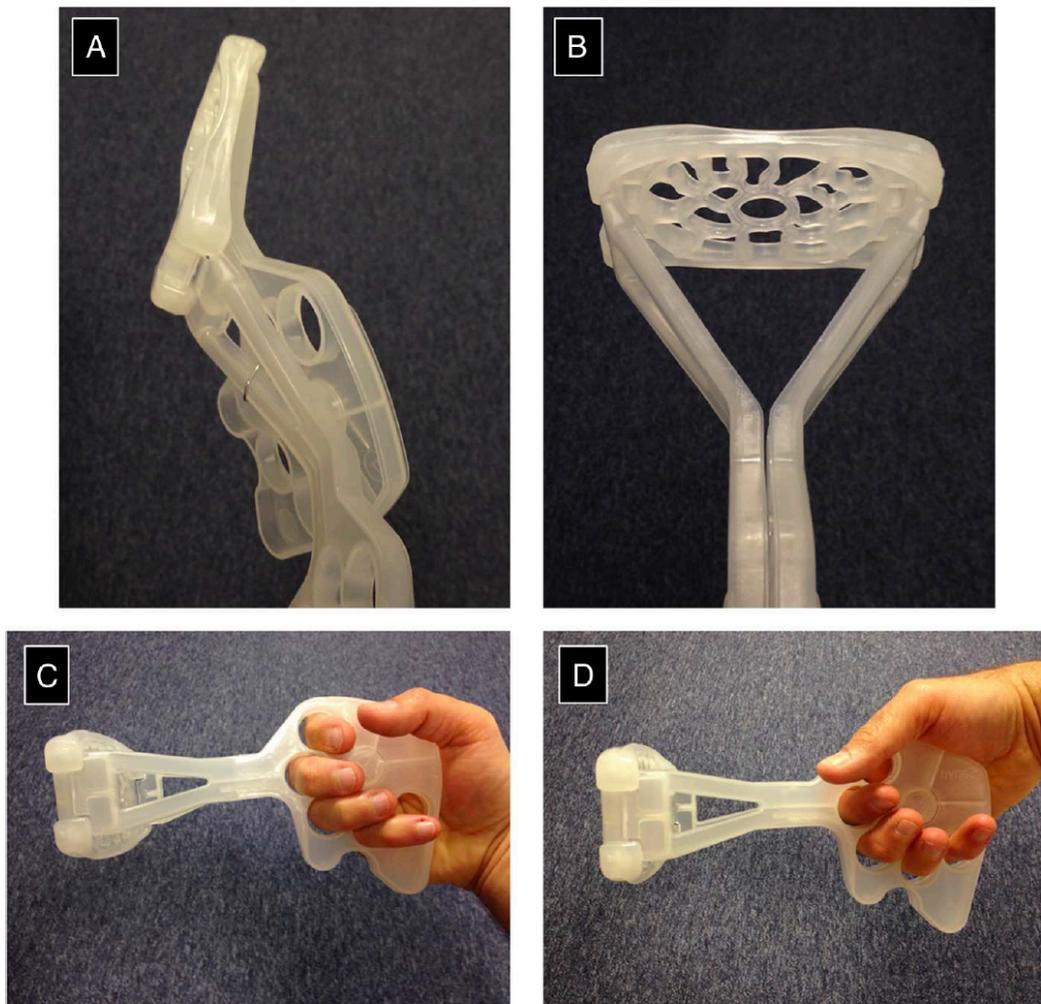
Since bimanual uterine compression is such an involved technique that must be sustained for a long period of time, researchers have been looking for ways to make it more manageable for birth attendants. One way is to use two care providers. This has the advantage of increased pressure and less fatigue of the providers, resulting in better and more sustained pressure. In a study done Andreatta et al. they compared the effectiveness of one provider performing bimanual uterine compression versus two people. Their results show that a single-provider is not as effective as a two-provider approach. Single providers were shown to provide appropriate compression for less than 2 minutes before

becoming fatigued. In the two-provider care approach, compression was properly sustained for 5 minutes before providers became fatigued.⁵¹ Using the two-provider approach does not necessarily mean there must be two skilled birth attendants present. The assistant providing external pressure on the fundus may be a family member or friend that can help under the supervision of the skilled attendant who will provide the internal pressure on the uterus. This technique could then be sustained for longer, leading to a greater chance of being able to stop the bleeding.

Another attempt to make bimanual uterine compression a less invasive procedure, is the creation of a device to take the place of the attendant's fist that provides the internal pressure. In a study done by Cunningham et al., they introduced a novel device called the PPH Butterfly device.⁴⁹ It is designed to be slim for insertion into the vagina, and then once inserted, it opens up to create a platform that will apply pressure to the uterus. The device has gone through a series of focus groups that have improved and evolved the product to the point where it is ready for testing in humans. The study also claims that the device could be used at an earlier stage of PPH to assist in diagnosing the cause of PPH if it is uncertain⁴⁹. If the pressure stops the bleeding, the etiology of PPH is atony. Whereas if the bleeding does not stop the source of hemorrhage is likely from vaginal lacerations (trauma). The platform design has large perforations in it to support stability, but also make it possible for blood to flow past it. If a flat platform was used it may block blood and clots from leaving the uterus, giving a false sense that the bleeding has stopped. If this device is proven to work effectively in humans and can be provided at a low cost, it may make bimanual uterine compression for effective and more likely to be used. With

the lack of uterotonics and supplies that are available in LMICs, physical procedures to manage PPH have a higher probability of being utilized.

Figure 4. PPH Butterfly device. The device in a flat insertable position (A). The triangular shape of the base of the platform gives it stability for pressure to be applied (B). The platform is locked into place when the handles are put together, the provider can then more easily stabilize it using the finger holes (C). The device may also be stabilized from above to correctly position the platform if the woman is more in a sitting position (D). Taken from Cunningham et al.⁴⁹



C. Intrauterine tamponade

One of the earliest forms of treatment for PPH was use of an intrauterine tamponade, most commonly done through uterine packing with sterile gauze.⁵² With the increasing discovery and effectiveness of uterotonics it has gradually been used less, although when it was used it had a high success rate for stopping bleeding. Currently, balloon technology has evolved to be used as a tamponade to control PPH. Originally engineered using a catheter with a balloon on the end filled with saline, a condom catheter has been developed to reduce costs and make the treatment available to LMICs.

The intrauterine balloon is thought to work by exerting pressure that is greater than the systemic arterial pressure, stopping blood loss from occurring.⁵² Most balloon catheters remain inserted for 24-48 hours to make sure the bleeding has truly stopped and a blood clot has formed. Foley catheters, traditionally used to drain the patient's bladder, were originally used as a uterine tamponade. Filled with 50-80 mL of blood, there are reports of it stopping bleeding after uterotonics failed to work. Concerned that the Foley catheter balloon was not large enough to be effective in the large volume of a postpartum uterus, studies showed success with the Sengstaken-Blakemore tube. This is a two-tube balloon traditionally used for the treatment of esophageal variceal bleeding. Since then there have been multiple other balloon shapes that have been suggested and used to more adequately fill the uterus cavity to provide apt pressure.

The condom-catheter is a low cost, accessible alternative for LMICs compared to the other types of balloon catheters. Condoms are often cheap and used as a part of family planning measures in clinics, making them readily accessible. The condom is tied with

silk to a Foley catheter and is then inserted into the uterus and inflated with saline. It is common to then pack the uterus with gauze to prevent it from slipping out of place. One disadvantage of the condom catheter is that it does not allow drainage of the uterine cavity. This can give a false sense that the bleeding has stopped, when in reality it is just filling the uterus. Other catheters have a drainage port that gives a more accurate picture of the amount of blood present and when bleeding stops.

A recent study looked at the effectiveness of the condom catheter in secondary hospitals located in Uganda, Egypt and Senegal. They did not find a decrease in maternal mortality in these settings when using the condom-catheter, but did find use of the condom catheter was associated with an increase in the cases of PPH-related surgery and maternal mortality.⁵³ Providers reported having an issue with the treatment in 24/48 cases (52.1%), 7 of the women's information was missing. A common problem reported was it taking more than one attempt to successfully insert the device and place the balloon. This study warrants the need for additional research and gives caution to relying on condom-catheters to treat PPH.

Intrauterine tamponade provides another line of intervention that can be tried before resorting to surgery. The decision of the intervention used is ultimately up to the skilled attendant present, being highly individualized and dependent upon the patient. Some patients may have less time for interventions and need to go straight to the operating room, while others may have a slower rate of decline and have time to try this less invasive approach. Its use in LMICs is still limited because of the need for an attendant to be present at birth and the need for materials that would be found in a hospital or clinic.

More research is needed to better look at the effectiveness of uterine tamponades and if it is a good option for remote community settings.

D. External aortic compression

External aortic compression is an emergency procedure that temporarily stops blood flow to the lower extremities, including the uterus. A bimanual approach is used to make sure cessation of blood flow is achieved.⁵⁴ One hand is placed on the upper thigh to feel for a femoral pulse and stays there for the remainder of the procedure. Once the femoral pulse is felt, the attendant's other hand is formed into a closed fist and placed just above the umbilicus. The fist is pushed down towards the patient's vertebral column with firm pressure. The femoral pulse should then no longer be felt, a sign that blood has been prevented from passing to the lower half of the body.⁵⁵

This procedure is most useful for temporary stopping the blood that is flowing to the uterus. Stopping the blood flow can give brief control of the bleeding to come up with a plan of action, place an IV or place a uterine tamponade. This technique has also been used for the management of abdominal-pelvic trauma cases. One study evaluated the effectiveness of bimanual external aortic compression during ambulance transfer. The results of the study showed the technique was effective for waiting for transport but not during transport. Participants of the study could apply firm and stable pressure for 20 minutes while stationary but failed to apply sustained pressure during transfer.⁵⁴ Since use of bimanual external compression only requires a trained attendant, it could be a quick, simple and lifesaving technique for the management of PPH in LMIC.

E. Uterine artery embolization

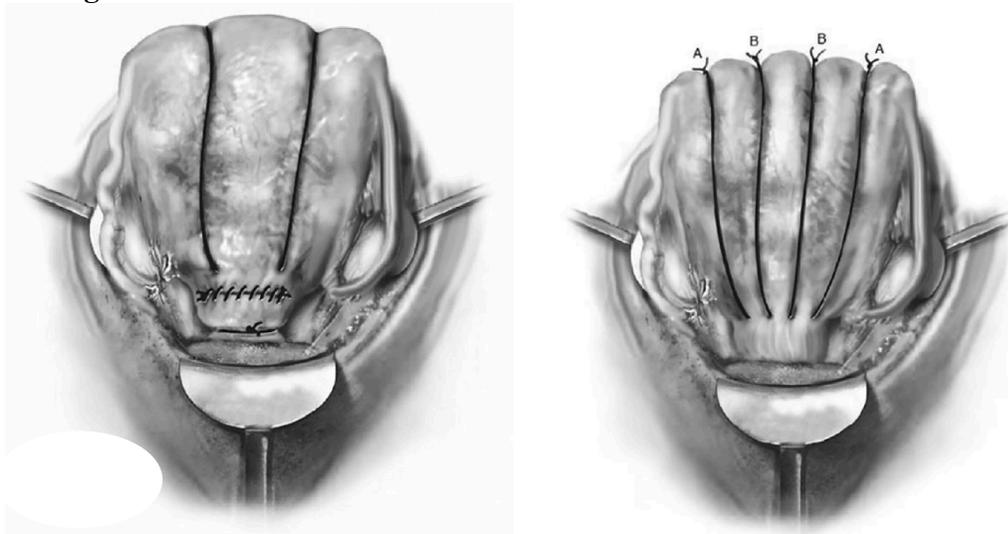
Uterine artery embolization is an angiographic procedure that involves inserting a catheter into the femoral artery and passing it into the uterine artery. A gelatin sponge is often the embolic material of choice because it allows temporary arterial occlusion and restores blood flow to the blocked area over the next few weeks.⁵⁶ This procedure has a high success rate, is less invasive than traditional surgery and preserves the fertility of the woman. If the woman is hemodynamically stable, with an interventional radiologist present, and near an angiographic suite with the appropriate equipment, the procedure should be considered.⁵⁷ This is not a feasible intervention in LMICs due to all the resources and personnel needed.

F. Uterine compression sutures

Uterine compression sutures are placed in the operating room to physically make the uterus contract to stop the bleeding. This intervention can be used to try and stabilize the patient before resorting to a hysterectomy. There are several different types of sutures that have been developed throughout the years. The B-lynch suture was the first uterine compression technique used for treating PPH. It involves performing a hysterotomy, if not already present, and then looping a suture from the hysterotomy site at the bottom of the uterus over the fundus, in order to apply external compression.⁵⁸ A study by Hayman et al. then reported that performing a hysterotomy to place B-lynch sutures is not necessary to place compression sutures.⁵⁹ They described a suture technique called

Hayman sutures, which does not require a hysterotomy. Sutures are applied from the lower part of the uterus and loop over the fundus to connect back to the bottom, giving the same external compression effect (Figure 5). Multiple suture loops can then be placed across the uterus to compress the entire surface of the uterus.

Figure 5. B-lynch and Hayman suture technique. Suture techniques for applying external uterine compression to treat PPH. Taken from Gilmandyar and Thornburg⁶⁰



Other suture techniques involve placing sutures in squares and adding transverse sutures in addition to the lateral sutures to give more compression to the uterus.⁵⁸ There have not been any studies conducted on the efficacy of which suture technique is best. The current recommendation of which should be used is individual to each patient and based on considerations such as site of bleeding, severity, and the experience of the surgeon performing the operation. This intervention has the ability to stop bleeding while keeping the fertility of the woman intact, and thus should be tried in patients who are stable before resorting to hysterectomy.

G. Peripartum hysterectomy (PH)

When fertility saving measures fail to stop the bleeding, it is necessary to resort to a hysterectomy to save the woman's life. The most common types of hysterectomies performed to stop PPH are a supracervical (SCAH) and total hysterectomy (TAH). The decision of which one should be performed is up to the surgeon and dependent on the present circumstances. A SCAH involves removing the upper part of the uterus while leaving the cervix intact and a TAH is the removal of the uterus and cervix. It is often faster to do a SCAH because the dilated cervix can be difficult to dissect and ligate the vessels.⁶⁰ There is also increased risk of injuries to the bladder and ureters while dissecting the cervix out in a TAH. Whatever approach is taken it is crucial to ligate the blood vessels to stop the bleeding fast.

In the case of LMICs, surgery is often not an option as there are no skilled facilities, limited skilled providers and a lack of tools available. This lack of definitive treatment makes prevention efforts that much more important. Preventing PPH before it gets unmanageable is the best way to reduce maternal mortality.

III. PREVENTION

Prevention of PPH is largely based on the identification of risk factors, treating those conditions if possible, and making an appropriate care plan. Once risk factors are detected the birth plan should advocate for a hospital birth if possible. This will give a greater chance that skilled care providers and necessary resources will be present in case

of any complications. This makes prenatal screenings vital to identify high risk pregnancies and make the necessary arrangements. During birth there are also specific precautions that should be taken to limit the occurrence of excess bleeding. Oxytocin and other uterotonics may be administered as a prophylactic measure at the beginning, or just after the birth of the baby. Having trained and prepared staff in the case of an emergency will give the patients the best outcome.

Prenatal care and use of ultrasound

Prenatal care should begin once a woman finds out she is pregnant, and then continue for the duration of her pregnancy. The WHO recommends at least 4 antenatal care (ANC) visits during pregnancy.⁶¹ ANC visits have been shown to be effective for prenatal screening and diagnosis and management of preeclampsia, each reducing the risk of adverse pregnancy and birth outcomes⁶².

Prenatal screenings are used to make sure the fetus is developing properly and there are no complications. Common tests done include blood, urine, glucose and blood pressure tests. Ultrasounds are a common diagnostic test used to look for any growth abnormalities or birth defects. Use of ultrasound during prenatal visits has been found to be effective for prevention of PPH mortality, specifically in the diagnosis of an abnormally invasive placenta⁶³. The ultrasound can be used to detect any biological risk factors that can increase the incidence of PPH⁶⁴. Ultrasounds have the power to diagnose polyhydramnios, multiple pregnancies, an invasive placenta and placenta previa, all risk

factors for PPH. This would allow the birth attendant to explain the delivery risks to the mother and advise that the birth takes place in a skilled facility.

However, availability of ultrasounds may be limited in some ANC settings in any given LMIC. This may be due to limited resources, limited training of health personnel or concerns about misuse, overuse and miscommunication⁶⁵. Further, some pregnant women may be reluctant to accept ultrasound services if they are not knowledgeable about its efficacy. Studies looking at how women in LMICs perceive use of ultrasound have reported a range of different perceptions. Some thought that having an ultrasound exam meant that there was a problem with the pregnancy, whereas others trusted the ultrasound to confirm the health and progress of the baby⁶⁶. Implementation of ultrasound technology must address these perceptions of the women who are intended to use the services.

A study done by Goldenberg et al. was one of the first studies to look at the impact of ultrasound technology on ANC in resource limited settings. The use of ultrasound technology was thought to be an incentive for women to attend ANC visits. They found that use of ultrasound did not increase the use of ANC visits or the number of hospital deliveries for women with pregnancy complications.⁶⁷ In a follow up study, the researchers conducted a survey to identify the factors that influenced women to attend follow-up visits and referrals. Results show that telling the women who to see at the hospital, how to get there, and what would happen led to an increased likelihood of going to the referral.⁶⁸ Good communication between the sonographer and the patient showed the best results for increasing care. Barriers reported include cost, transportation,

distance, not knowing where to go and being turned away at the hospital. Increasing ANC visits is not solely dependent on technology and tests that can be provided to the woman. This study shows that there is a larger social and educational piece to it, requiring communication between the providers and the patients.

ANC visits are also important for diagnosis of preeclampsia, a condition characterized by new onset hypertension and proteinuria after 20 weeks of gestation. Blood pressure screenings are regularly performed to look out for hypertension. Complications of preeclampsia include poor fetal growth, placental abruption, seizures, preterm birth, and organ damage. High blood pressure during pregnancy reduces the amount of blood and nutrients that can pass through the placenta, putting the life of the fetus at risk.⁶⁹ If diagnosed early on in the pregnancy and it is not too severe it can be treated with medication and the fetus will be carefully monitored for the rest of the pregnancy. If diagnosed close to the due date, the provider may recommend induction of labor or a caesarean section. The goal of management of preeclampsia is to keep blood pressure in a normal range and prevent any other complications from occurring. This requires frequent care visits for the patient to be continually monitored.

If preeclampsia is not under control during delivery, the high blood pressure makes it more likely that bleeding will occur. It will occur faster and there will be a larger amount of blood lost due to the increased pressure. In addition, it is thought that angiogenic factors found in the blood are associated with a greater risk of preeclampsia.⁷⁰ There is a decrease in the amount of angiogenic factors available in the blood, which causes systemic endothelial dysfunction leading to the development of preeclampsia.

Angiogenic factors are also an important part of the clotting system, increasing the amount of blood lost. Getting preeclampsia and any other risk factors under control before delivery will decrease the risk of PPH and increase the preparedness of the birth attendants if it does occur.

Active management of the third stage of labor

Taking certain precautions during labor have been proven to lower the risk of bleeding, especially in high risk patients. There are two management techniques for the third stage of labor: expectant and active management. Expectant management of the third stage of labor is a hands-off approach that relies on the body's own physiological mechanisms to deliver the placenta. Any aid given is usually by gravity and sometimes by maternal pushing efforts. No uterotonic drugs are given and the cord is usually not clamped or cut until the placenta has been delivered. In active management of the third stage of labor, the physician intervenes to help with the delivery of the placenta.⁷¹ First a uterotonic agent is delivered before, during or right after childbirth to facilitate uterine contraction for separation of the placenta. The cord is then clamped and cut to allow for use of cord traction to deliver the placenta. Uterine massage is then used after delivery of the placenta to stimulate uterine contractions to restrict the spiral arteries. Use of a uterotonic immediately after birth is one of the greatest preventative measures and can be used on its own with no other interventions. AMTSL is used in an attempt to reduce the amount of blood loss during placental delivery, reducing the chance of PPH.

The recommendation for use of the AMTSL comes with relatively weak evidence of its usefulness. Most of the studies have been done in high income countries where

uterotonics and other interventions are readily available if bleeding does occur. Thus, the approach taken is often expectant management of the third stage of labor until a problem occurs. With the lack of resources in LMICs, active management may be more appropriate to use to prevent PPH. A study done by Stanton et al. looked at the use of AMTSL in seven developing countries and saw varied results among the countries. They found that the use of a uterotonic drug was nearly universal, but the use of uterine fundal massage was not utilized in most countries.⁷² The lack of uterine massage was suggested to be a result of insufficient surveillance of women after birth when most maternal deaths occur. The study also reported incorrect implementation of the AMTSL, suggesting a lack of training and education of the necessary health care providers.

A study done by Tenaw et al. assessed the knowledge and practice of care providers using AMTSL in South Ethiopia. They found that only 37.7% of the care providers had knowledge of the AMTSL practices.⁷³ The observation of the use of the interventions was also not satisfactory and calls for more in-service training. The study called attention to the need for universities and health science colleges to revise their course contents to enhance the skills of their graduates. In Tanzania, a cross-sectional study was conducted to evaluate the effectiveness of competency-based training to increase use of AMTSL for prevention of PPH. The training focused on implementing the three main interventions in the correct order and at the right time: administration of a uterotonic within 1 minute of birth, use of controlled cord traction and uterine massage. Results show a significant improvement in the practice of AMTSL, increasing overall PPH prevention.⁷⁴ There was a greater increase in lower-level facilities compared to

larger hospitals. This has thought to be because of the lower turnover rate of staff in lower-level facilities compared to hospitals. This study shows promising results for what quality training and implementation of AMTSL can look like in low resource settings to help prevent PPH.

These prevention strategies all hinge on the acceptance and use of medicine and healthcare. This starts with education and empowerment. The more people know, the more they will be empowered to take control of their health decisions. Using people in the community as role models is one way to bridge this gap. At the same time logistical measures must also be taken to increase providers and resources to low income countries. This will require people from different areas working together towards the common goal of reducing morbidity, mortality and increasing quality of life.

IV. PROPOSED SOLUTIONS

Reducing the occurrence of PPH and maternal mortality involves increasing resources and people's access to healthcare. Implementing the prevention strategies for PPH requires a skilled birth attendant to carry them out, which there is a shortage of. The proportion of births attended by a skilled health provider is one of the indicators used for monitoring the millennium development goal number 5, improvement of maternal health. In 2014 more than 71% of births were attended by a skilled provider, an increase from 59% in 1990.⁷⁵ Although the national average of attended births has increased, the proportion of attended births in LMICs is below 50%.⁷⁶ This shortage of healthcare

workers leaves many women at home, delivering their babies alone and with little help if there are any complications. There is a need for more people, more training and more social change moving forward to increase access to healthcare.

Community health workers and volunteers

Prior studies conducted in LMICs found that pregnant women interacting with community health workers (CHW) during pregnancy had increased access to maternal and newborn health services compared to pregnant women who did not interact with these workers⁷⁷. CHWs are people from a community, employed to perform specific healthcare tasks to help the people in their community.⁷⁸ Community health volunteers (CHV) may perform the same tasks but are volunteering their time and may receive incentives to do so. Health services may be preventative, promotive or curative in nature and have been shown to provide a similar or greater level of care compared to skilled providers. Tasks may include immunizations, prenatal care, human immunodeficiency virus (HIV)/ acquired immunodeficiency syndrome (AIDS) support and distribution of bed nets. These workers have the ability to offer informal health services when access to a formal type of care is not available, or not accepted. With proper training, oversight and implementation, the use of community health workers and volunteers can bring healthcare access to the most remote areas of the world.

One of the main reasons CHWs are so effective in low resource settings is because they are trusted and accepted by the people they aim to help. As members of the community they have relationships with the people and are seen as a credible source of

information. They also set an example to the people of the community by implementing the skills they are teaching. Even under less than ideal conditions the CHWs still manage to positively increase health behaviors of their community.⁷⁹ These workers are often underpaid, lacking resources and not well supervised, but are still able to make a difference. This is in part due to the unique motivations they have for serving. In a study that looked at the effectiveness of CHWs, the results showed that most workers saw their service as a calling that they liked to do. In addition, the workers saw their service as a way to empower people in their communities rather than just treat them like the view of formal bureaucratic healthcare organizations.⁷⁹ The social role that the CHW holds is so important that the study postulated that a CHW would not be effective outside of their own community. This requires individual recruitment, selection, and training for each community.

Selection and training of CHWs is different in each country but the worker should be someone living in the community who is also approved by the community. This guarantees a degree of authority and respect that workers will get from the community. Other qualifications vary based on the task list of the worker. Some may be required to read, write and do basic math while others just need to be of a certain age to meet the qualifications.⁷⁸ In some countries CHWs are given less tasks and are seen as a placeholder until ‘real’ healthcare providers can come. Recently the WHO has begun ‘task-shifting’ as a way to allow more medical skills and procedures to be performed by community health workers. Better training and utilization of these workers and volunteers is necessary to increase their effectiveness. The shared motivations of these workers

suggest recruitment of CHWs in other communities should not be hard. Expanding the number of CHWs will help increase healthcare access when skilled providers are absent. And in areas where there is an established health system, CHWs can increase use of these services through education and advocating for them.

Maternal community health workers are used to connect women to services, increase deliveries in primary healthcare facilities and deliver antenatal services. These workers are vital to newborn and postnatal care as well. They help with the breastfeeding process, any postnatal bleeding and the immunization of the children.⁸⁰ The attitudes towards and the effectiveness of CHWs in LMICs has been studied in a few countries. One in Nigeria found mixed reviews about stakeholders perceptions on the work of CHWs. These stakeholders were chosen based on their knowledge and experience working with different community health worker groups. Mixed reviews were found on the work done by CHWs. Some stakeholders viewed them as having an important role in bringing health information to their communities. Others thought that they could be doing more and both views are probably true. The stakeholders were also asked for their opinion on introducing community midwives to bring skilled providers to the area. There was concern that introducing community midwives in the same spaces as CHWs may result in a duplication of roles and disharmonious work environment.⁷⁷ They suggest that employment of the CHWs, re-training them and introducing more aspects of midwifery to them may be a better option for increasing skilled care to women.

The use of CHWs provide a vital role in overcoming social barriers to providing healthcare. They are not fully skilled providers and they should serve in their scope of

practice as outlined by their training. As training becomes more skill oriented, task-shifting to these workers will be able to take place. Even if the role of CHWs was based on education and passing of information, they could still help prevent health problems and get people to seek the help they may need from a skilled provider. Whether task shifting occurs to CHWs or not, there is still a need for skilled providers to be available when there are complications that require more invasive interventions.

Skilled birth attendants

Similarly to CHWs, skilled birth attendants (SBA) have been shown to increase the delivery of maternal health services in underserved areas⁸¹. Skilled birth attendants are recognized as people with formal training, such as midwives, nurses and physicians, that know how to manage normal pregnancies, childbirth and the immediate postnatal period. With less than 50% of births in low income countries being attended by skilled providers, we simply need more people. This will require better training and education efforts to encourage people to seek out this career opportunity. One good place to draw from are the community health workers if they are interested in more schooling and training. Another group of people in these countries that may be recruited are traditional birth attendants (TBA).

Before the implementation of a formal healthcare system many women received care from traditional birth attendants. These were older and well-respected women that had experience helping with childbirth. Becoming a TBA happened through mentorship by an older TBA or through self-teaching. With the establishment of a formal healthcare

system and training, skilled birth attendants were recognized only as midwives, nurses, and physicians. TBAs have no formal training and are not recognized by the healthcare system as skilled providers, yet in 2016 22% of pregnant women worldwide delivered with the help of a TBA.⁸² Even if TBAs are not trained as SBA, their ability to provide support and company to the women help them in a new environment. They often are the link that connect women with the appropriate healthcare facilities.⁸³

Beyond distance, transportation, and cost barriers that prevent people from accessing care, there are also several other social and emotional barriers that prevent access. A study done in Ethiopia to collect information about these barriers found that women perceived SBAs as having low quality, unfriendly, abusive care and that there was a large number of male SBAs who are culturally inappropriate.⁸⁴ There was also a strong preference to give birth at home with a TBA present. These cultural mores add an extra layer of complexity to increase the number of births attended by providers. This is when education and empowerment become important so people can change and better their lives on their own accords.

Life Course Approach

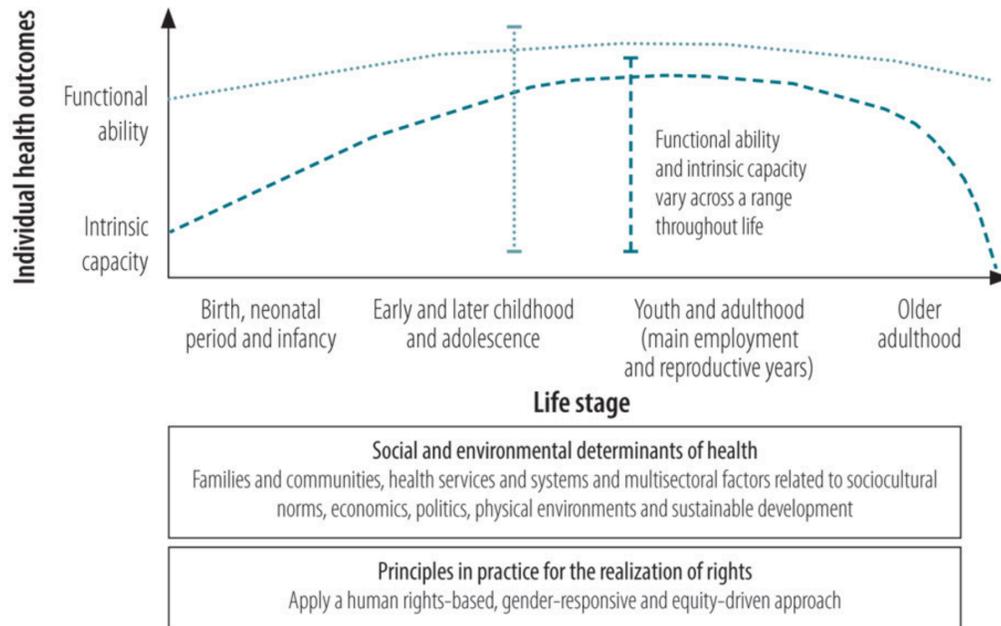
In an attempt to lower rates of PPH, and maternal mortality in general, it is important to look at more broad scale interventions, like the life course approach. The life course approach is a way of thinking that looks at an individual's health from a more holistic perspective. It considers all experiences since birth and looks at genetics, environmental factors, and socioeconomic conditions. The goal is to optimize people's

well-being and empower them with the realization of their rights.⁸⁵ With the roots of this theory coming from psychology and sociology, the person is looked at in terms more than just their medical diagnosis. Most studies have focused on non-communicable diseases but can be extended to all health areas⁸⁶. By definition, this approach is more culturally competent and gives a long-term, longitudinal approach to care.

Specifically, in maternal and child health this approach looks at the peri-conception period for environmental exposures, maternal health prior to pregnancy and ways to strengthen mother-child interactions. Reducing the maternal mortality will also in turn decrease the child mortality rate. Having a healthy mother to care for the baby will give the child a better chance of survival and appropriate development. Teaching a child, the importance of healthcare from a young age may also stop the cycle of people not using healthcare. In the future, this can lead to more births taking place at health facilities with skilled birth attendants present.

Figure 6 shows the conceptual framework for this approach, showing the functional and intrinsic ability of people. Intrinsic abilities account for the person's physical and mental capacities, whereas the functional ability includes the intrinsic ability plus the environment they live in.⁸⁵ This approach requires big changes in policy, healthcare, investments, measurements and monitoring, that can take years to construct or re-construct⁸⁷. Moving forward in fighting PPH, maternal mortality and all other health problems, this approach should be the framework for building a sustainable healthcare system.

Figure 6. Life course approach to health. Diagram showing the health outcomes of individuals at different stages of life based on rights and health determinants. Taken from Kuruvilla et al.⁸⁵



V. CONCLUSION

There have been great strides taken in reducing the occurrence of PPH and the maternal mortality, but that work needs to continue and expand in the coming years. The technology and medicine have been created, the next step is getting it to the people who need it most. This paper has looked at the risks, interventions, prevention strategies and potential solutions to treating PPH in limited resource environments. The approach needs to be multifaceted to help people currently at risk for hemorrhage, but also to create a sustainable healthcare system to end the perpetuation of disease and increase health for all.

Short-term, the best intervention strategy is to use AMTSL during delivery of the child and using misoprostol as the uterotonic agent of choice when oxytocin is not available. Actively managing the third stage of labor is relatively non-invasive, consisting of a uterotonic, controlled cord traction and uterine massage. This should be used whenever there is a skilled birth attendant present who is trained to provide this care. Increased access and administration of misoprostol should be used in places where there are currently no uterotonics, there are no skilled birth attendants present and oxytocin is unavailable. Misoprostol comes in a tablet form that can be given to women at prenatal visits to self-administer after birth. It is heat stable, eliminating storage concerns, and it would allow for women who give birth in remote areas without a birth attendant to have some type of treatment if needed. Although the side effect profile is greater and it is less effective than oxytocin, it would give them a chance at survival.

Long-term, there needs to be training initiatives to increase the skills of current birth attendants and to train new people. Both CHWs, skilled birth attendants and traditional birth attendants have the potential to be trained in different skills to reduce the risk and manage any cases of PPH. CHWs play a large role in education and acceptance of the healthcare that is present. They can work to educate their communities on the importance of prenatal screenings and giving birth in a skilled facility. Both skilled and traditional birth attendants have a lot of knowledge already and are providing care to these communities. Increasing their skills and coverage area will help to increase women's access to having a birth attendant present.

Healthcare reform is the big picture goal of many of these nations, in order for their people to obtain affordable and acceptable care. This is a larger feat to tackle due to the many layers involved such as international relations, governments, politics and cultural expectations. The life course approach should be a guide for creating a healthcare system that focuses on a person throughout their entire lifetime. The health that a mother gets will affect her child, and the health that child receives will affect the care that their future children receive. The perpetuation of this cycle needs to stop to save and improve the lives of all people in LMICs.

LIST OF JOURNAL ABBREVIATIONS

Acta Obstet Gynecol Scand	Acta Obstetrician et Gynecologica Scandinavica
Annu Rev Pathol Mech Dis	Annual Review of Pathology: Mechanisms of Disease
Aust N Z J Obstet Gynaecol	Australian and New Zealand Journal of Obstetrics and Gynaecology
BJOG: Int J Obstet Gy	BJOG: An International Journal of Obstetrics and Gynaecology
BMC Health Serv Res	BMC Health Services Research
BMC Pregnancy Childbirth	BMC Pregnancy and Childbirth
BMJ Innov	BMJ Innovations
Br J Haematol	British Journal of Haematology
Bull World Health Organ	Bulletin of the World Health Organization
Drug Deliv and Transl Res	Drug Delivery and Translational Research
Glob Health Sci Pract	Global Health: Science and Practice
Hum Resour Health	Human Resources for Health
Int J Gynecol Obstet	International Journal of Gynecology and Obstetrics
Matern Child Health J	Maternal and Child Health Journal
PLoS Med	PLoS Medicine
Reprod Health	Reproductive Health
Syst Rev	Systematic Reviews
Ultrasound Obstet Gynecol	Ultrasound in Obstetrics and Gynecology

World J Surg

World Journal of Surgery

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CURRICULUM VITAE

