CELOX™ PPH

UTERINE HAEMOSTATIC TAMPONADE

CLINICAL AND SCIENTIFIC **MONOGRAPH**

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FOREWORD

As an obstetrician I have witnessed firsthand the many challenges and risks associated with childbirth. A positive birth experience can quite quickly develop into an emergency within a few minutes. One of the most pressing concerns for both healthcare providers and patients is the risk of postpartum haemorrhage (PPH), a condition that can occur after delivery and result in serious complications, including maternal death. PPH can be exacerbated in cases of non-hospital births, due to the absence of skilled professionals, proper medication, and surgical facilities, resulting in potentially more severe outcomes.

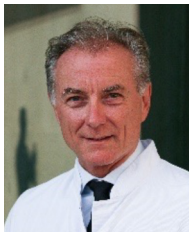
Despite the availability of several treatment options to manage PPH, there is still a need for innovative solutions that can quickly and effectively control bleeding, especially in low resource communities and settings where such solutions are needed the most. With more than three decades of experience at Germany's largest maternity hospital, I have gained valuable insights into the most effective treatments for PPH. CELOX™ PPH is a groundbreaking solution that addresses this life-threatening condition and marks a significant milestone in our efforts to enhance maternal care and improve clinical outcomes.

CELOX™ PPH's key advantage is its rapid action in stopping bleeding, a crucial factor in treating PPH where time is of the essence. In my role as an obstetrician, I recognise that quick action can make all the difference in the outcome for our patients. Numerous studies have demonstrated that CELOX™ PPH can stop bleeding within minutes, independently of the body's natural clotting process, which can help prevent additional complications.

As healthcare professionals, we are always looking for tools that require minimal training. CELOX™ PPH is designed to be simple to apply, following a standard uterine packing technique, that can be readily utilised by trained healthcare practitioners. This can be particularly important in emergency situations, where time is limited, and the pressure is high.

More than a decade of clinical evidence has demonstrated CELOX™ PPH to be a safe and reliable option for managing PPH and stopping bleeding quickly. Furthermore, our own extensive clinical experience and publications over the last 7 years have shown that CELOX™ PPH is highly effective in the control and treatment of uterine PPH and avoids further surgical interventions.

CELOX™ PPH represents a significant step forward in the management of PPH and I am confident that by incorporating CELOX™ PPH into our obstetric practices, we can help to ensure that women receive prompt and effective treatment in the event of PPH, ultimately saving countless women's lives worldwide.



I hope that this clinical monograph will serve as a valuable resource for healthcare professionals around the world and that it will help raise awareness about the value of CELOX™ PPH in the treatment of PPH.

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EXECUTIVE SUMMARY

Maternal mortality is a significant global concern with approximately 295,000 maternal deaths occurring worldwide. Postpartum Haemorrhage (PPH) is a leading cause of maternal mortality and is defined as severe bleeding that occurs after giving birth. While primary PPH typically occurs within 24 hours of childbirth, secondary PPH can present itself as late as 12 weeks after childbirth. The most common cause of PPH is insufficient uterine contractions after childbirth due to uterine atony. If left untreated, PPH can evolve into a critical emergency situation, with the potential to induce hypovolemic shock and organ failure. Each year, around 14 million women experience PPH resulting in about 80,000 maternal deaths globally. The prevalence of PPH varies significantly across the world, ranging from 7.2% in Oceania to a staggering 25.7% in Africa.

There are a variety of approaches available for managing PPH. As per the recommendations by the World Health Organization (WHO), the initial steps following diagnosis include uterine massage, the administration of uterotonics (with oxytocin being the preferred option), and the initiation of fluid replenishment using isotonic crystalloids. Should bleeding prove difficult to manage despite these initial interventions or if uterotonics are not accessible, it is advisable to consider uterine balloon tamponade. In cases involving ongoing haemorrhage, uterine artery embolization is recommended and resources permit. However, in situations where bleeding continues despite the administration of uterotonic medications and the application of conservative measures, prompt surgical intervention becomes essential. Recently, a product called CELOX™ gauze, initially designed for military and emergency services to address severe injuries that are associated with substantial blood loss and high mortality rates, has been adapted for obstetric application, as CELOX™ PPH, and has proven successful in treating PPH.

The primary objective of this document is to comprehensively assess and present the scientific and clinical evidence supporting the use of CELOX™ PPH in the management of PPH. This evaluation is specifically focused on substantiating the claims made as part of the Medical Device Regulations (MDR) and Conformité Européene (CE) mark approval process. These claims include:

- Achieving 100% haemostasis for grade 1 and 2 bleeding (up to 2500mls) in all delivery scenarios.
- Demonstrating 94.3% haemostasis for grade 1 to 3 bleeding (up to 8000mls) in all vaginal deliveries.
- Evidencing a 78% reduction in the necessity for hysterectomies when compared to the current standard of care.
- Establishing its safety and user-friendliness, with minimal product training requirements.

This monograph presents a comprehensive compilation of scientific evidence, encompassing laboratory experiments and animal studies. These findings unequivocally endorse the efficacy of CELOX™ PPH in initiating blood coagulation across a spectrum of experimental models, even in cases with compromised clotting due to anticoagulation. Additionally, the document features an array of clinical studies, demonstrating that CELOX™ PPH consistently facilitates rapid and effective haemostasis in patients experiencing various levels of PPH.

1. World Health Organisation - 2019

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1. INTRODUCTION

Section key points

- Maternal mortality estimated at 223 per 100,000 live births across 185 countries
- Thirty-four percent of estimated global maternal deaths caused by Haemorrhage, including postpartum Haemorrhage
- It has been recommended that there needs to be a concerted effort to reduce PPH using cost-effective, resource-appropriate interventions, and to reduce the need for expensive surgical interventions

CELOX™ PPH is a uterine haemostatic tamponade that has CELOX™ haemostatic chitosan-based granules loosely adherent to a gauze fabric material (Figure 1), which provides rapid and effective control of postpartum bleeding. Originally developed for use by military and emergency services, CELOX™ PPH has recently been awarded Conformité Européene (CE) mark approval for the management of uterine PPH.

Figure 1. CELOX PPH, a uterine haemostatic tamponade

Women tragically lose their lives due to complications arising during and after pregnancy and childbirth. A substantial portion of these complications originates during pregnancy and, importantly, is preventable or manageable. Some preexisting conditions may also exacerbate during pregnancy, particularly when not adequately addressed as part of a woman's care. Notably, uncontrolled bleeding has been identified as a critical factor contributing to heightened maternal morbidity and mortality (Marietta et al, 2006) and is associated with a substantial rise in healthcare costs (Stokes et al, 2011; Corral et al, 2015). PPH is commonly defined as excessive bleeding from the genital tract, specifically an amount of blood loss exceeding 500 ml within the first 24 hours after giving birth (World Health Organization, 2012a).

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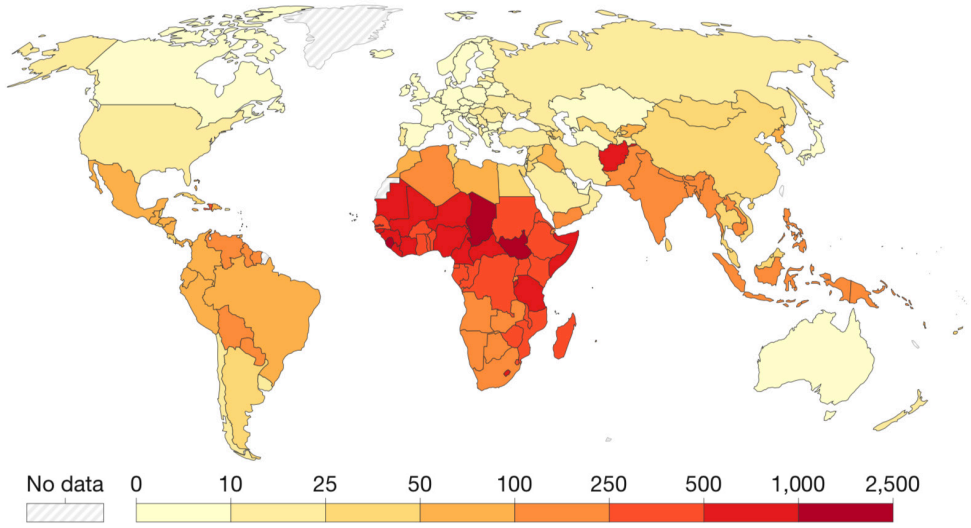
Maternal mortality during pregnancy, defined as the death of a woman while pregnant or within 42 days of delivery or termination of pregnancy (Muñoz et al, 2019), has been estimated as being in the region of 295,000 maternal deaths globally, indicating a maternal mortality ratio of 223 per 100,000 live births across 185 countries (World Health Organization, 2019). According to a systematic review, it was found that approximately 34% of the global maternal deaths were caused by haemorrhage (GBD 2015 Maternal Mortality Collaborators, 2016). The majority of these deaths occur in low-income countries, for example, in Sub-Saharan Africa and Southern Asia (accounting for 86% of all maternal deaths) (Dol et al, 2022) (Figure 2). Women in high-income countries also continue to die from major obstetric haemorrhage (Knight et al, 2009; Ford et al, 2015; MBRRACE-UK, 2021). Severe bleeding is one of several complications that account for 75% of all maternal deaths (Appendix 1, Table 1), with the remainder being caused by or associated with infections such as malaria or related to chronic conditions such as cardiac diseases or diabetes (Say et al, 2014).

Figure 2. The worldwide maternal mortality ratio*, 2020 (source: OurWorldInData)



*The maternal mortality ratio is the number of women who die from pregnancy-related causes while pregnant or within 42 days of pregnancy termination per 100,000 live births.

PPH is a leading cause of maternal mortality worldwide, affecting approximately 14 million women and resulting in 80,000 deaths each year (Borovac-Pinheiro et al, 2018). It has been recommended that there needs to be a concerted effort to reduce PPH using cost-effective, resource-appropriate interventions, and to reduce the need for expensive surgical interventions (Escobar et al, 2022).

CELOX™ PPH is a uterine haemostatic tamponade intended to be used as a physical haemostat for the control of emergency bleeding. This monograph describes the clinical condition of PPH and its treatment. The monograph will then go on to summarise CELOX™ technology, CELOX PPH™ and summarise the scientific and clinician data in support of the use of CELOX™ PPH in the treatment of PPH.

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2. POSTPARTUM HAEMORRHAGE (PPH)

Section key points

- PPH represents a critical condition characterised by severe bleeding that typically arises within a timeframe spanning from 24 hours to 12 weeks after childbirth and is a main cause of maternal mortality.
- The global prevalence of PPH ranges from 7.2% in Oceania to as high as 25.7% in Africa. Each year, approximately 14 million women experience PPH, leading to an estimated 80,000 maternal deaths across the globe.
- PPH is a serious condition that, when left untreated, can result in severe consequences, including complications related to blood transfusions, hysterectomy, disseminated intravascular coagulation (DIC), consumptive coagulopathy, multi-organ failure, organ failure, hypovolemic shock and death.
- PPH is defined as an estimated blood loss exceeding 500 ml. Severe or secondary PPH is defined by a loss of 1000 ml, while massive, life-threatening PPH is attributed to a blood loss exceeding 2500 ml or the presence of hypovolemic shock.
- There are a wide variety of risk factors that contribute to the occurrence of PPH, including a previous history of PPH, uterine inversion, delivery-related trauma of any cause, placenta praevia, placental abruption, uterine rupture, and multiple gestation.
- A primary cause of PPH is uterine atony (insufficient contraction of the uterus following childbirth).

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2.1. Definition of PPH

PPH is heavy bleeding following childbirth, categorised as either primary PPH or secondary PPH. Primary PPH is characterised by a blood loss of 500 ml or more within the initial 24 hours after birth, and it can range from minor (500-1000 ml) to major (more than 1000 ml) (Bell et al., 2020; Wormer et al., 2022). Secondary PPH occurs when abnormal or heavy bleeding occurs between 24 hours and 12 weeks after childbirth, often after leaving the hospital (Bell et al., 2020; Wormer et al., 2022). Given the absence of a universally accepted definition for PPH (Abdul-Kadir et al., 2014; Leal and Lança, 2022), the Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis (NATA), in collaboration with the International Federation of Gynaecology and Obstetrics (FIGO), the European Board and College of Obstetrics and Gynaecology (EBCOG), and the European Society of Anaesthesiology (ESA), has recommended defining primary PPH as blood loss exceeding 500 ml within 24 hours, regardless of the mode of delivery. Severe PPH is further characterised by ongoing blood loss exceeding 1000 ml within 24 hours, while massive, life-threatening PPH involves blood loss exceeding 2500 ml (Appendix 1, Table 2) (Muñoz et al., 2019).

2.2. Incidence of PPH

Defining the incidence of PPH, and comparing results of studies, is hampered by the lack of a standardised approach to blood loss assessment (Rath, 2011). Visual estimation, although widely used, is inaccurate and is often associated with under-reporting of actual blood loss, especially in cases of large volumes of PPH (Bell et al, 2020). Systematic reviews confirm that the incidence of PPH is higher with quantitative measurement, as opposed to visual estimation with inaccurate reporting leading to inaccurate estimation of incidence and severity of PPH (Calvert et al, 2012; Caroli et al, 2008; Deneux-Tharaux et al, 2014). A systematic review between 1997 and 2002 reported an incidence of PPH exceeding 500 mL, with subjectively assessed blood loss at 7.2% and quantitatively assessed blood loss at 10.4% (Caroli et al, 2008). A French study, utilising quantitative measurement of blood loss, revealed a rate of PPH exceeding 500 mL at 10.5% (Deneux-Tharaux et al, 2014). In an international systematic review, a higher prevalence of 14.2% was reported (Calvert et al, 2012). In this latter systematic review, the prevalence of PPH (≥500 ml) ranged from 7.2% in Oceania to 25.7% in Africa (Appendix 1, Table 3).The prevalence of severe PPH (≥ 1000 ml) was highest in Africa at 5.1% and lowest in Asia at 1.9%.An incidence of PPH (≥500 ml) 30.9%-40.7% was measured in Wales in 2017 where quantitative measurement was started at delivery (Bell et al, 2020), and other studies reported the incidence of PPH ≥500 ml to be 33.7% in the UK (Briley et al, 2014) and in Australia 22% (Flood et al, 2018). A prospective cohort study in Wales, found the incidence of PPH of >1000 ml, >1500 ml and >2000 ml was 8.6%, 3.3%, and 1.3%, respectively (Bell et al, 2020).

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Systematic reviews indicate that the incidence of PPH exceeding >1000 ml, as determined through quantitative blood loss measurement, falls within a range of 2% (Deneux-Tharaux et al, 2014) to 4.2% (Calvert et al, 2012). In a Swedish study, the rate of bleeds exceeding >1000 ml was reported at 4.7% (Baldvinsdóttir et al, 2018). It's noteworthy that these results are approximately 50% lower than the 8.6% figure recently documented in a cohort study conducted in Wales (Bell et al, 2020).

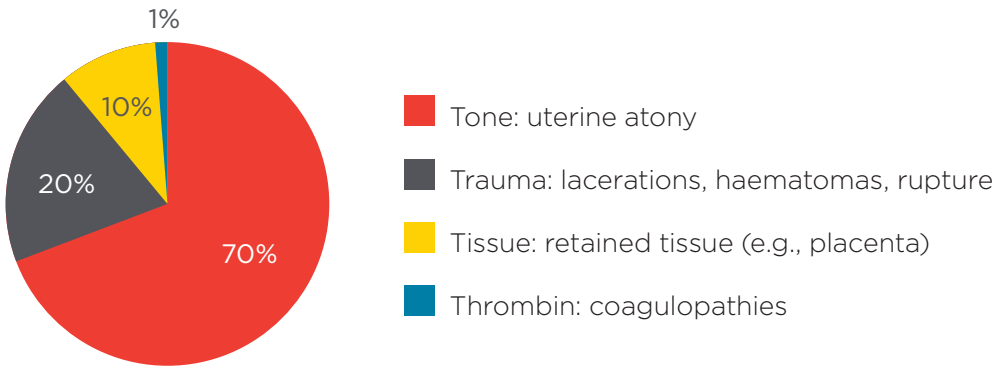
Furthermore, meta-regression analyses conducted by Calvert et al (2012) have suggested that the method used to measure blood loss significantly influences prevalence estimates for both PPH and severe PPH. The marked variation observed in the incidence and prevalence data underscores the critical role played by the method of PPH measurement, whether it is subjective or quantitative.

2.3. Causes of PPH

During pregnancy uterine blood flow increases throughout gestation and, at term, blood flow can be 7-times pre-pregnancy levels. This physiological response to pregnancy increases the risk of massive bleeding after delivery (Hofer et al, 2023). Physiological changes in the mother to prepare for blood loss and placental separation after childbirth (e.g., changes in haemostasis) and an imbalance of these physiological processes can lead to PPH (Gill et al, 2021).

A large majority of PPH cases are categorised as primary PPH. Secondary PPH is a less common form of PPH compared with primary PPH (see above for definitions).

Figure 3. Causes of PPH (adapted from Evensen et al (2017))



Primary PPH: The main causes of primary PPH can be categorised by the "Four Ts" mnemonic ("Tone", "Trauma", "Tissue", and "Thrombin") (Evensen et al, 2017) (Figure 3):

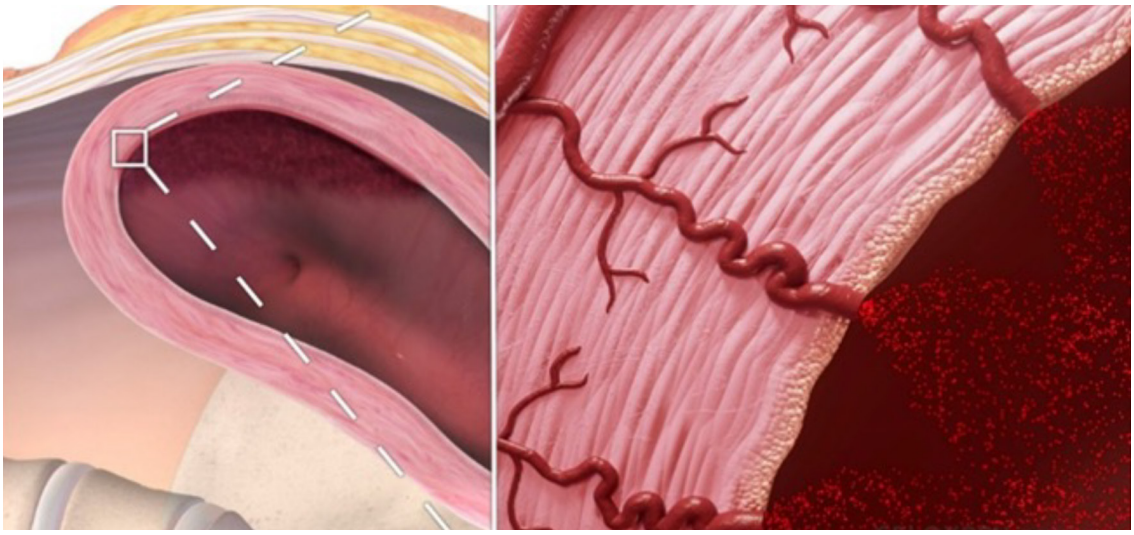
- **Tone (uterine atony):** Uterine atony, is the most common cause of PPH and is characterised by a softness and/or weakness of the uterus. This occurs when there

is a failure of the uterine muscles to contract effectively, thereby hindering the closure of blood vessels at the site where the placenta was attached, as illustrated in Figure 4 (Breathnach and Geary, 2009).

- **Trauma:** Genital tract trauma, including the uterus, cervix, and/or vagina, stands is the second most common cause of PPH. Injury to these tissues during or following childbirth can lead to substantial bleeding due to their heightened vascularity during pregnancy.
- **Tissue:** Retained products of conception, specifically the placenta, or the presence of blood clots is the third most common cause of PPH. On average, the time from delivery to placental expulsion is reported to be 8-9 minutes (Magann et al, 2005a). Prolonged intervals between delivery and placental expulsion have been linked to an elevated risk of PPH (Magann et al, 2005b).
- **Thrombin:** Coagulation disorders, although uncommon as a cause of PPH, can significantly impact the body's ability to form blood clots, potentially leading to uncontrollable bleeding, even from minor injuries. Such abnormalities can be either congenital or acquired (Lippi et al, 2012; Neuenfeldt et al , 2021).

Secondary PPH, a less frequent form of PPH, shares causative factors with primary PPH. Common culprits of secondary PPH encompass retained placenta, infection, and subinvolution of the placental site. Rarer triggers involve bleeding disorders, uterine artery pseudoaneurysm, and cervical carcinoma (Wormer et al, 2022).

Figure 4. Uterine bleeding resulting from the failure of the uterus to contract and naturally occlude placental blood vessels following childbirth.



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2.4. Diagnosis of PPH

The diagnosis of PPH begins with the recognition of excessive bleeding and a thorough patient assessment to determine its underlying cause (Evensen et al., 2014). To monitor cumulative blood loss, a quantitative measurement is performed by weighing blood-soaked pads, sponges, clots, and any associated surgical drapes. Normally, healthy pregnant women can endure a blood loss of 500 to 1000 ml without displaying signs or symptoms (Magann et al., 2005b). In cases of excess bleeding, whether from the vagina or directly from the uterus during a caesarean section, the Four T's mnemonic (Figure 3) can be employed to pinpoint specific causes (Evensen et al., 2017).

Symptoms associated with PPH, may include tachycardia as one of the earliest signs, followed by low blood pressure, sweating, fainting, pallor, reduced urine output, and difficulty breathing (Evensen et al., 2017) (Refer to section 2.3)..

Without prompt treatment, PPH can rapidly deteriorate, leading to hypovolemic shock, organ failure, and maternal mortality (McDougall et al., 2022).

2.5. Risk factors for PPH

The risk factors for PPH are influenced by the specific cause of the haemorrhage (Wormer et al, 2022) (Refer to Appendix 1, Table 4). Factors that increase the risk of uterine atony include having a high number of previous pregnancies, experiencing previous instances of PPH, fetal macrosomia (giving birth to a large baby), encountering difficulties in progressing through the second stage of labor, having a prolonged third stage of labor, and undergoing general anesthesia (Royal College of Obstetricians and Gynaecologists, 2016). Trauma-related risk factors involve injuries to the genital tract resulting from tears in the cervix, vagina, or perineum after spontaneous vaginal delivery or operative delivery. Additionally, there can be extensions and lacerations during a caesarean section due to improper positioning or the baby being deeply engaged in the pelvis. Another risk is uterine rupture, which can happen if there has been previous surgery on the uterus. Uterine inversion can occur due to excessive traction on the umbilical cord resulting in the uterus turning inside out (Royal College of Obstetricians and Gynaecologists, 2016). Additionally, the presence of coagulation disorders adds to the risk (See Appendix 1, Table 4). While identifying these risk factors can assist in recognising women at the highest risk of PPH, it's important to note that 20% of PPH cases occur in women who don't display any of these risk factors (Magann et al, 2005b).

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2.6. Prevention of PPH

PPH is predominantly seen as a preventable and manageable condition, underscoring the vital significance of promptly identifying and intervening to improve maternal outcomes.

The majority of current solutions to treat PPH depend on women giving birth in settings equipped with prompt access to surgical and intensive care resources. These solutions are not appropriate for use in low-resource settings, such as LMICs –the regions with the highest mortality rates and the greatest need for effective treatment solutions. (Evensen et al, 2017)

The third stage of labour is the time from the birth of the baby to the expulsion of the placenta and membranes (Begley et al, 2019). There are two approaches to handling the third stage of labor: active management (AMTSL) and expectant or physiological management.

- **Active management**: The administration of uterotonic medication (e.g., oxytocin) after the delivery of the baby, early clamping and cutting of the umbilical cord, and controlled umbilical cord traction until separation and delivery of the placenta
- **Expectant management:** This is the "leave well alone approach"; there is no administration of uterotonic medication, the umbilical cord is not clamped or cut until after cessation of pulsating (stopped delivering blood to delivered baby), allowing separation of the placenta without intervention, and the placenta is delivered by gravity or spontaneously by maternal expulsion.

Evidence suggests that AMTSL reduces the risk of PPH by 60% (Prendiville et al, 2000; Leduc et al 2009). More recently, a Cochrane Review on the evidence for active versus expectant management for women in the third stage of labour found that there was an absence of high-quality evidence. The review of the available data suggested that the data "appeared to show" that active management reduced the risk of severe primary PPH greater than 1000 ml at the time of birth (Begley et al, 2019). The review further concluded that, for all women, irrespective of their risk of severe bleeding, active management may reduce severe bleeding. Active management is standard practice in the UK, Australia, and New Zealand. However, due to the increasing influence of midwifery, expectant or physiological management is now often used by midwifery practitioners, (Harrison, 1998). On the other hand, expectant or physiological management of the third stage is widely favored in Northern European countries and certain regions of the USA and Canada. It is also the preferred approach for in-home childbirth practices in New Zealand. The practice of AMTSL varies among providers (Schorn et al, 2017), and recommendations differ among professional organisations worldwide (Dahlke et al, 2015).

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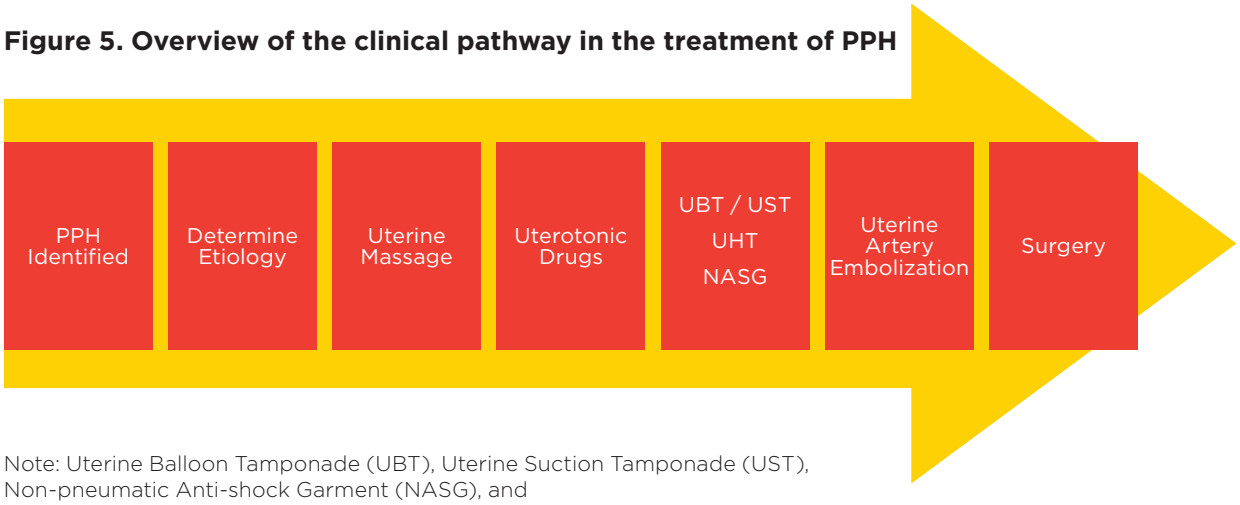
The International Federation of Gynecology and Obstetrics (FIGO) is actively contributing to the global effort to reduce maternal death and it has proposed a series of recommendations – based upon the World Health Organization's (WHO) own recommendations – for the prevention of PPH (Appendix 1, Table 5).

2.7. Treatment of PPH

The field of obstetrics lags behind other medical specialties in terms of technological innovation. A recent study, which evaluated innovation levels based on patent data and venture capital funding, revealed that obstetrics exhibited the least innovation when compared to cardiology, orthopaedics, gastroenterology, ophthalmology, and dermatology (Kogutt and Satin, 2020).

Treatment strategies for PPH typically follow a progressive sequence from less invasive to more aggressive approaches. These strategies include compression techniques, medications, various procedures, and, in extreme cases, surgical interventions (Likis et al, 2015). Additionally, PPH management may include therapies like the administration of blood and fluids and the use of anti-shock garments. Figure 5 summarises an overview of a clinical pathway for the treatment of PPH.

Figure 5. Overview of the clinical pathway in the treatment of PPH



Note: Uterine Balloon Tamponade (UBT), Uterine Suction Tamponade (UST), Non-pneumatic Anti-shock Garment (NASG), and Uterine Haemostatic Tamponade (UHT)

In the majority of cases, PPH is addressed as an obstetric emergency, with the primary objective being to quickly identify and arrest the underlying cause of bleeding. The key goals in treating PPH are the prompt cessation of the bleeding source and the restoration of blood volume. Table 6 (Appendix 1) summarises some of the main treatments used for PPH.

Uterotonic drugs (e.g. oxytocin) are the first-line treatment for PPH when prevention fails and excessive bleeding occurs (Voillequin et al, 2022). Second-line treatment options for PPH are summarised in Table 7 (Appendix 1), and Figure 6 shows an example of a treatment algorithm for treatment of PPH due to uterine atony (Rath et al, 2012).

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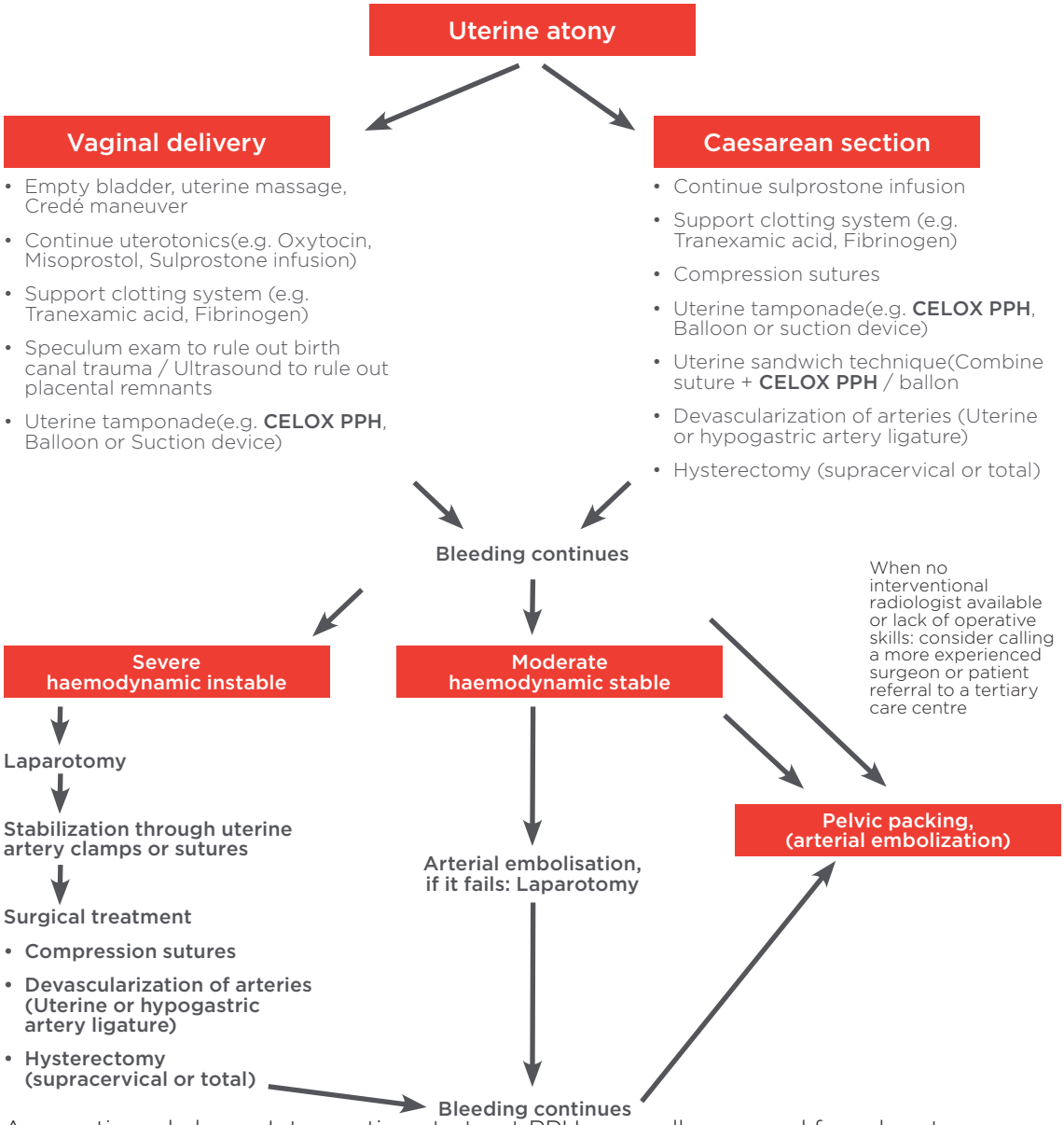
Figure 6. Treatment Algorithm for PPH Due to Uterine Atony (Rath et al, 2012, modified by Henrich et al, 2023).



As mentioned above, Interventions to treat PPH generally proceed from less to more invasive and include a number of different treatments. Below is a summary of PPH treatments:

- **Uterine massage:** Recommended as soon as PPH is diagnosed, and is commenced alongside fluid replacement. Uterine massage to the woman's lower abdomen encourages the uterus to contract both during and after delivery of the placenta.
- **Empty the bladder:** A full bladder can impede uterine contractions. Empty by using an intermittent catheter or indwelling catheter (left in place).
- **Bi-manual compression:** The clinician places one hand on the abdomen and the other hand inside the vagina, then compresses the uterus between the two hands This technique encourages the uterus to contract, treats uterine atony, and assists

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with the expulsion of retained placenta or blood clots.

- **Medical management (e.g. uterotonics):** Uterotonic medications induce uterine contractions and enhance uterine tone, effectively countering uterine atony.
- **Uterine Haemostatic Tamponade (CELOX™ PPH):** Involves the insertion of gauze through the vagina to effectively fill the uterine cavity until gentle resistance is encountered. This historical technique primarily applies controlled pressure to the uterine wall, effectively arresting bleeding. However, it's important to note that advancements have introduced a novel approach: gauze coated with proprietary chitosan-based haemostatic granules agents. This innovation operates a unique mode of action at the bleeding site, employing mechanisms that go beyond simple compression to achieve haemostasis (as described in Section 2.8). The gauze is later removed by carefully grasping and gently pulling on the end that remains outside of the vagina.
- **Uterine Balloon Tamponade (UBT):** The procedure involves inserting a deflated balloon device through either the vagina or abdomen (in the case of a caesarean section) into the uterine cavity. Once in place, the balloon is filled with sterile fluid via a syringe, exerting controlled pressure on the uterine walls to halt bleeding. Subsequently, the balloon is removed by connecting a syringe to the inflation port and withdrawing the sterile fluid to deflate it. The balloon's tail, which remains outside the vagina, is then carefully grasped and gently pulled for removal.
- **Uterine Compression Suturing (e.g. B-Lynch):** Apposes the anterior and posterior uterine walls through a pair of vertical brace sutures that encircle the uterus. This technique effectively compresses the uterine cavity, reducing bleeding and promoting uterine contraction.
- **Uterine Artery Embolization (UAE):** One or more embolising agents (e.g. absorbable gel particles, foam, metal coils) are injected into the uterine arteries to reduce blood flow.
- **Surgical Approach:** Surgical procedures come into play when alternative less invasive treatments have proven ineffective. Hysterectomy, typically considered a last-resort option, is only pursued when all other alternatives have been explored and found ineffective.
- **Non-Pneumatic Anti-Shock Garment (NPASG):** This segmented device is securely fastened around a woman's legs, pelvis, and abdomen, exerting controlled pressure. By directing blood towards the heart, lungs, and brain, it effectively prevents or manages shock. Particularly valuable in low- and middle-income countries (LMICs), the NPASG facilitates patient transfer to proper medical facilities.

To maximise quality of care and achieve optimal outcomes for women with PPH, the utilisation of guidelines and clinical care pathways offer the most effective treatment approach. These treatment aids are based upon best practice and best available evidence in order to identify, prevent, and manage PPH (International Federation of Gynecology and Obstetrics, 2022).

The International Federation of Gynecology and Obstetrics (FIGO) has proposed a number of recommendations – based upon WHO's own recommendations – for the treatment of PPH (Appendix 1, Table 7).

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2.8. Chitosan-derived gauze

Section key points

- Chitosan is a natural polysaccharide with a good safety profile
- Chitosan-derived polymers are novel haemostatic agents
- Chitosan-derived haemostatic agents initiate haemostasis independent of platelets and coagulation factors
- Chitosan-derived haemostatic agents are effective haemostats in coagulation-compromised patients

A relatively recent option for the uterine packing tamponade is gauze coated with materials that promote clotting and haemostasis. These temporary external haemostats, or "haemostatic dressings", (Schreiber and Neveleff, 2011) are designed to be applied topically, and to be removed once haemostasis has been achieved. Originally developed for military use, they are increasingly being used in the hospital setting (Schreiber and Neveleff, 2011).

Chitosan-derived haemostats have been used for a range of clinical situations in hospital settings (Seyednejad et al, 2008) and have a particularly good safety profile (Baldrick, 2010; Waibel et al, 2011). Chitosan refers to a series of polymers derived from crustacean chitin and is a complex carbohydrate that is biodegradable. Chitosans have widespread applications, are very biocompatible and have a very good safety profile (Baldrick, 2010; Waibel et al, 2011; Singh and Ray, 2000).

Chitosan has no intrinsic haemostatic properties and works independently of platelet activation and the coagulation system (Yang et al, 2008; Bennett et al, 2014). The haemostatic properties of chitosan appear to be by direct electrostatic interaction between positively-charged chitosan-derived material polymers and negatively-charged cell membranes of the red blood cells which may account for its haemostatic activity (Mirzadehl et al, 2002; Millner et al, 2010). The chitosan-derived material's ability to bind red blood cells (RBCs) promotes the immobilisation of RBCs and the formation of an adherent gel clot (Bennett et al, 2014). The absorption of blood plasma by chitosan-derived materials may also lead to concentration of blood cells and promoting haemostasis via the formation of a haemostatic plug, and red blood cell aggregation (Chung et al, 2016; Chou et al, 2003; Pogorielov and Sikora, 2015). Chitosan-derived materials have also been shown to encourage platelet adhesion and activation (Xia et al, 2022). This aligns with the suggestion that biomaterials may influence how proteins

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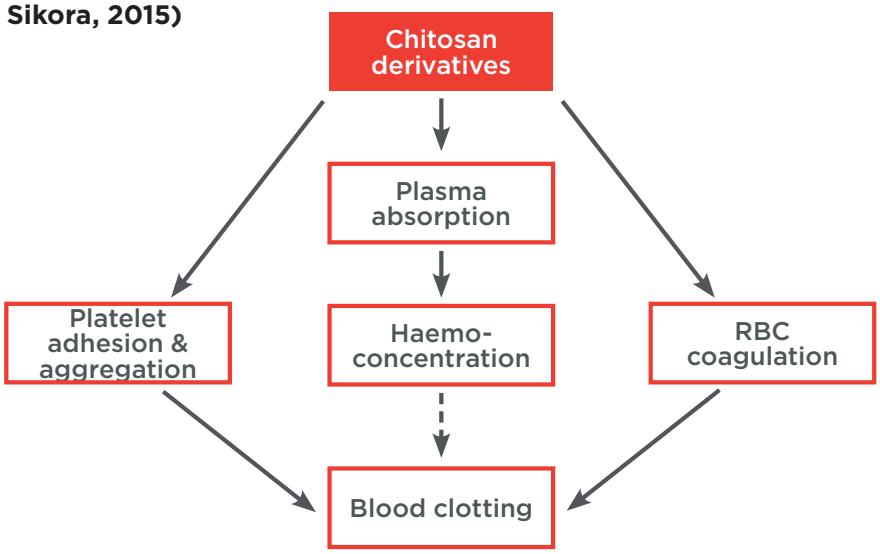
absorb and orientate on surfaces leading to a modulation of cellular responses in areas such as haemostasis (Lord et al, 2011). Figure 7 summarises the haemostatic effects of chitosan-derived materials. This dual mechanism forms a cross-linked 'pseudo-thrombus' that adheres to the surrounding tissue and plugs the bleeding site (Rao and Sharma, 1997). These properties suggested chitosan-derived materials as potential materials as haemostats, leading to their use in dressings and other haemostatic devices (Kozen et al, 2008; Millner et al, 2009).

Figure 7. Haemostatic effects of chitosan derivatives (adapted from Pogorielov and Sikora, 2015)



2.9. Pathogenic challenges to haemostasis

Haemostasis after injury that leads to a cessation of blood loss is a complex process. Coagulopathy is a condition in which the blood's ability to form clots is impaired (Hunt, 2014), and can result in dangerously excessive bleeding. Impaired blood clotting can arise due to a number of reasons; coagulopathies (e.g. Von Willebrand disease, platelet functional disorder or congenital hemophilia), chronic diseases (e g , cancer, chronic liver disease, or renal disease), medications (e g , heparin, warfarin, and aspirin) or disorders such as disseminated intravascular coagulation (DIC) (Kim et al, 2021)

Coagulopathies in pregnancy can present or lead to obstetric emergencies and can vary from prothrombotic/microangiopathic conditions such as DIC (Disseminated Intravascular Coagulopathy), TTP (Thrombotic Thrombocytopenia Purpura), HELLP (Hemolysis, Elevated Liver Enzymes, Low Platelets), to Deep Venous Thrombosis (DVT), recurrent Pregnancy losses and bleeding events such as antepartum haemorrhage (APH) and PPH (Bhave, 2019).

Anaemia, one of the most common complications in pregnancy, significantly impacts the risk of PPH. This observation is particularly significant given that more than a third of all pregnant women encounter anaemia (Brenner et al., 2022).

During the early stages of pregnancy, blood volume surges, progressively increasing throughout pregnancy, ultimately reaching an average elevation of 45% above pre-pregnancy levels. While blood cell production rises, the growth surpasses the red blood cell mass, resulting in what is termed "physiological anaemia" (Sanghavi and Rutherford, 2014). Simultaneously, fetal development escalates the demand for iron, leading to common iron-

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deficiency anaemia in pregnant women (Raut and Hiwale, 2022).

Consequently, anaemic women cannot endure the same degree of blood loss as their healthier counterparts. This unique physiological aspect highlights the necessity for careful medical attention and interventions to mitigate the heightened risks that anaemia poses during and after childbirth.

The vulnerability of PPH intensifies in anaemic women due to compromised clotting, reduced uterine contractions, slower recovery, and disrupted blood volume regulation, accentuating the need for vigilant medical attention for pregnant individuals with anaemia to manage complications during and after childbirth. In a recent study, PPH risk stood at 6.2% for moderate anaemia defined as a haemoglobin concentration of 70-99 g/L) and 11.2% for severe anaemia (defined as a haemoglobin concentration of less than 70 g/L). Severe anemia correlated with a sevenfold increase in the likelihood of death or near miss, underscoring anaemia's profound influence on PPH and its consequences. (WOMAN-2 trial collaborators, 2023).

Mechanisms through which anaemia causes PPH.

- Anaemia increases the heart rate and cardiac output and increases blood loss from bleeding vessels. As haemoglobin falls, aortic hypoxia-sensing cells activate the sympathetic nervous system, increasing heart rate and stroke volume to maintain oxygenation. (Weiskopf et al, 2003).
- Anaemia increases blood flow from bleeding vessels due to reduced blood viscosity. Blood viscosity depends on the number (and volume) of red cells in the blood. Blood viscosity falls with decreasing haematocrit and as blood viscosity falls, blood loss increases. (Nygaard wt al, 1935). (Whittaker et al, 1933).
- Anaemic blood clots are more susceptible to fibrinolysis. Red blood cells increase the resistance of fibrin blood clots to fibrinolysis in a dose-dependent manner.(Wohner et al, 2011).
- Anaemia prevents platelet margination and increases bleeding time. In normal flowing blood, red cells are concentrated in the centre of the vessel and platelets are concentrated by the wall. This is laminar flow. If a blood vessel is ruptured the platelets at the wall form a platelet plug. Anaemia disrupts laminar flow and increases the bleeding time. (Aarts et al 1988) (Anand et al, 1994).
- Anaemia (or more specifically iron deficiency) may directly cause uterine atony. Iron is essential for the normal functioning of enzymes with vital cellular functions. It is essential for enzymes and proteins involved in oxidative metabolic processes (e.g., mitochondrial energy metabolism) and is especially important for cells with a high energy demand (cardiomyocytes and skeletal cells). Iron deficiency causes muscle weakness and fatigue. It has also been suggested that anaemia might cause uterine atony from impaired uterine oxygenation. (Nair et al, 2016).

Summary by Professor Ian Roberts, Professor of Epidemiology at the London School of Hygiene and Tropical Medicine

2.10. Chitosan and coagulopathic bleeding

Effective haemostasis "independent of blood status" is needed to reduce the occurrence of post-operative complications related to coagulopathic bleeding (Kim et al, 2021), and this is equally applicable for postpartum situations such as PPH. Chitosan-derived haemostats can overcome the challenge of coagulopathic bleeding because of the material's coagulation pathway-independent mechanism of action (Yang et al, 2008). As a result of this independence, chitosan-derived haemostats can act in the presence of anticoagulants (Croisier and Jérôme, 2013; Klokkevold et al, 1999). Furthermore, chitosan-derived materials have been shown to be an effective haemostat in patients with coagulopathy (Misgav et al, 2017).

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3. CELOX™ PPH

CELOX™ PPH is a gauze coated with a proprietary chitosan derivative composition that incorporates chitosan in the form of high-surface-area granules, strategically engineered to achieve optimal effectiveness in managing bleeding.

3.1. Mechanism of action

The mechanism of action for CELOX™ PPH is a multi-step process critical to its haemostatic effectiveness. This process begins with the absorption of fluids from the blood, causing CELOX™ PPH granules to swell and take on a gel-like consistency. Subsequently, a direct electrostatic interaction unfolds between the positively charged CELOX™ PPH granules and negatively charged red blood cells. This interaction effectively traps red blood cells within the gel, resulting in the formation of a robust mechanical clot that acts as a plug, sealing the bleeding placental bed blood vessels (Figure 8). Furthermore, the CELOX™ PPH gauze adheres to the surrounding tissue through mucoadhesion, anchoring the gel clot securely in place. This mechanism establishes a physical barrier that effectively arrests bleeding, thereby reducing the likelihood of rebleeding. CELOX™ PPH's application can be sustained for up to 24 hours before removal (Figure 9). Importantly, CELOX™ PPH operates independently of the body's natural clotting mechanisms, making it highly effective even in patients with coagulation disorders or those taking blood-thinning medications. Moreover, it maintains the gel plug, ensuring sustained haemostasis while allowing for the natural clotting process to take place. Originally developed for military trauma applications, CELOX™ PPH's unique mechanism of action makes it a valuable tool for achieving haemostasis in challenging clinical scenarios (Millner et al. in 2011).

Figure 8. Formation of gel-like clot as blood contacts CELOX™ PPH

Blood from bleeding placental bed vessels comes into contact with CELOX™ PPH packed into the uterus (A) Swelling of CELOX™ PPH and trapping of red blood cells occur, resulting in the formation of a robust mechanical gel-like clot (B) Negatively charged red blood cells are attracted to positively charged CELOX™ PPH granules (C) which leads to haemostasis. CELOX™ PPH is applied to the uterine fundus once it is confirmed that there are no placental remnants or clots left in the uterus (see Figure 9).

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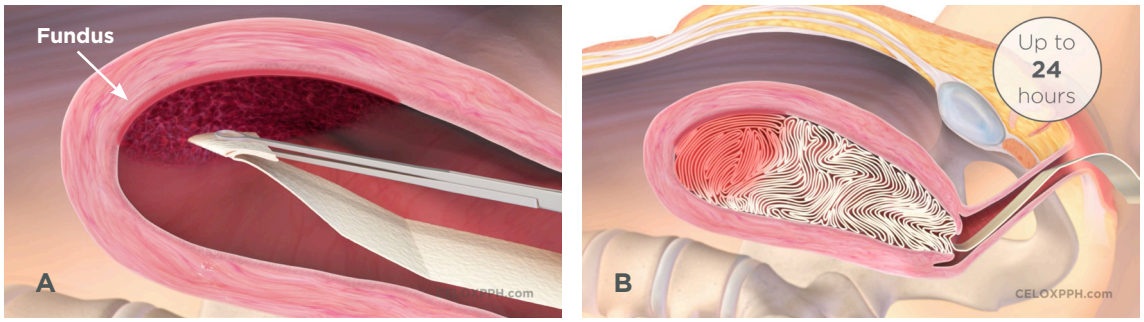
Figure 9. Application of CELOX™ PPH at site of Haemorrhage



Application of CELOX™ PPH at the fundus of the bleeding uterus (A). CELOX™ PPH is removed up to 24 hours after initial application (B), and after haemostasis has occured.

Indication for use

CELOX™ PPH is intended to be applied and removed vaginally to provide control and treatment of uterine postpartum haemorrhage when conservative management is warranted.

Contraindications

- Subjects who present with uterine rupture.
- Unresolved uterine inversion.
- Current cervical cancer.
- Current purulent infection of the vagina, cervix, uterus.
- Ongoing Pregnancy.

Warnings

- Do not use if the primary pack is damaged or open as the device may not be sterile.
- Keep away from liquids prior to use. The CELOX™ granules will gel in contact with liquid, making application difficult and reduce haemostatic effectiveness.
- As with other haemostatic agents, do not aspirate blood into cell saver equipment or autologous blood salvage circuits. There is a potential risk of embolism if the blood is returned to the patient.
- The haemostatic effect of CELOX™ PPH is not enhanced by the addition of topical thrombin, the activity of which may be destroyed by the pH of CELOX™ PPH.
- CELOX™ PPH must not be used as a vaginal/cervical pack for uterine postpartum haemorrhage as uncontrolled bleeding could continue in the uterus.
- For single use only. Re-use could potentially result in the risk of infection and lack of device performance.
- If the patient develops high fever (>38°C) following haemostasis remove the device.
- Do not leave CELOX™ PPH for longer than 24h in the body due to possible risk of infection.
- Transvaginal application of CELOX™ PPH may not be possible when cervix dilation has not started e.g., in case of elective c-section.
- Do not use suturing techniques (e.g., uterotomy closure, B-Lynch, Pereira) whilst CELOX™ PPH is in the uterus as this may result in CELOX™ PPH being incorporated into the suture causing difficulty for removal and risk of product tearing.

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4. SCIENTIFIC AND CLINICAL EVIDENCE FOR CELOX™ PPH

Section key points

- Significant level of evidence supporting CELOX™ PPH as an effective haemostat
- Laboratory studies show rapid clot formation in normal and coagulation-deficient blood, and in hypothermic blood when using chitin-derived materials
- Chitosan-derived materials are effective haemostats in a number of pre-clinical models of uncontrolled and coagulopathic bleeding
- Clinically, CELOX™ PPH has been shown to be an effective haemostat in PPH, leading to a reduction in the rate of hysterectomy
- CELOX™ PPH has the potential to provide cost-saving benefits

This Scientific and Clinical Monograph will present in more detail the evidence supporting the use of CELOX™ PPH, a chitosan-derived gauze supporting its use in the treatment of PPH.

4.1. Literature review methodology

Search of internet reference databases (e.g., PubMed/MEDLINE, PubMed Central, Europe PMC, The Cochrane Library, the National Institute for Health and Clinical Excellence (NICE)) were undertaken to identify published articles related to the scientific and clinical evidence for the use of CELOX™ PPH in the treatment of PPH.

The search included articles published between January 1970 and November 2022. In addition, manual searches of peer-reviewed journals and conference proceedings of relevance to PPH treatment and not catalogued in reference databases were also performed. Search keywords included “chitosan”, “CELOX™ PPH”, “postpartum”, and “obstetrics”.

Articles identified were excluded during a manual review if they were unrelated to the subject device, indications for use, safety, or performance.

4.2. Pre-clinical studies

Several studies have been conducted to demonstrate the effectiveness of chitosan (wound dressings) in promoting blood clotting in haemostatic and coagulopathic animal models as well as laboratory assessments, as summarised in Table 8 (Appendix 1)

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4.3. Clinical Evaluations

On a global scale, PPH emerges as the primary contributor to maternal mortality, as emphasised during the World Health Organization's (WHO) Postpartum Haemorrhage (PPH) Summit in 2022. Calvert et al. (2012) reported that this condition, defined as blood loss exceeding 500ml, is estimated to affect a range of 7.2% to 25.7% of women globally.

Numerous strategies have been introduced to address the critical issue of excessive blood loss during childbirth. Notably, a recent advancement in obstetric care is CELOX™ PPH, a chitosan-derived haemostatic gauze, that effectively serves as a uterine tamponade. This innovative solution, when combined with its potential to stimulate local haemostasis within the uterine cavity, holds significant promise for the management of PPH.

The initial investigations into the haemostatic properties of chitosan predominantly involved laboratory animals and demonstrated highly favorable outcomes (Table 8 of Appendix 1). Historical studies involving human subjects primarily focused on military personnel in conflict zones (Alam et al, 2005, Pozza and Millner, 2011 and Arul et al, 2012).

A study that investigated traumatic injuries in civilians involving 160 patients treated with chitosan, found that chitosan resulted in faster haemostatic control compared to a conventional compression bandage, with no adverse effects (Hatamabadi et al, 2015). Other uses are being developed, including the maintenance of haemostasis during surgery (Huang et al, 2015) or in the prevention of recalcitrant epistaxis (Kourelis and Shikani, 2012).

Numerous clinical studies have been published, demonstrating the clinical efficacy of CELOX™ PPH in treating PPH. The subsequent section will delve into these studies, and concise summaries of each of these papers are provided in Appendix 1 for reference.

In a recent Expert Review featured in the American Journal of Obstetrics and Gynecology (AJOG) Henrich et al (2023) provided a comprehensive summary of the key evidence supporting the application of chitosan-covered tamponade for managing PPH. The review highlighted the effectiveness of chitosan-covered tamponade in stopping therapy-resistant PPH, reducing hysterectomies, and blood transfusions. Based upon the evidence, the review recommended that hospital and outpatient birth attendants should consider having chitosan-covered tamponade available and ready for use, and should be included as a second line intervention or adjunct in management protocols for PPH. The review also includes a link to an instructional video offering a step-by-step guide for intrauterine application of chitosan-covered tamponade in order to optimise effectiveness and safety.

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Table. Summary of clinical studies for CELOX™ PPH in PPH pt1

Reference	Device (Manufacturer)	Study details	Study results	Additional comments
Biele et al (2022) [Article] (Section 4.3.4)	• CELOX™ PPH (Medtrade) • Balloon tamponade (Cook Medical)	• A database retrospective cohort study • Patients with PPH (who delivered at a university hospital between May 2016 and May 2019) • N=666 • CELOX™ PPH N=85 • Study Objective: To compare the effectiveness of CELOX™ PPH in comparison to balloon tamponade and medical therapy alone. • The primary outcome was the need for surgical/radiological therapy including compressing sutures, selective devascularization, (re-) laparotomy and HE. • Secondary outcomes were differences in hemoglobin levels, duration of inpatient stay, admission to intensive care unit, number of administered blood products and inflammation parameters	• There were no significant differences in the need for surgical therapy • A significantly lower number of hysterectomies in the CELOX™ PPH group than in the balloon tamponade group.	• There were no relevant differences in secondary outcomes and no adverse events related to the CELOX™ PPH . • Since the introduction of chitosan tamponade, the number of PPH related hysterectomies dropped significantly by 77.8%
Carles et al (2017) [Article] (Section 4.3.9)	• CELOX™ PPH (Medtrade) • Chitosan powder • Chitosan powder+ CELOX™ PPH (Medtrade)	• Case studies • Variety of uterine-related bleeding conditions • N=4 (CELOX™ PPH or chitosan+ CELOX™ PPH, N=3) • Study objective: Describe the use of CELOX™ PPH to treat life-threatening obstetric bleeding	• Uterine bleeding halted within five minutes using CELOX™ PPH • CELOX™ PPH removed without difficulty	• CELOX™ PPH is not mentioned by name, but device description suggests CELOX™ PPH • Conclusion: Cases of severe uterine bleeding resolved using CELOX™ PPH
Henrich et al (2023) Retrospective Data Analysis Report V1.1 – 19 May 2022 (Section 4.3.1)	• CELOX™ PPH (Medtrade)	• Retrospective analysis • Patients with PPH (uterine, vaginal, cervical) not controlled by conventional means • N= 102 (full set population, "FAS" group) (N=91, a subset of patients with a clear indication of uterine bleeding only, "UBPP" group) • Study objective: To evaluate the performance and effectiveness in management of PPH • Primary outcome: Hemostasis without surgical intervention • Secondary outcome: Level of adverse events, ability to remain in situ for up to 24 hours	• Primary outcome: CELOX™ PPH halted blood loss in 89.2% (91/102) FAS patients, and 91.2% (83/91) UBPP patients. CELOX™ PPH reached 100% successful hemostasis in all UBPP patients with grades 1 and 2 (significant blood loss levels). For grade 3 (life-threatening blood loss), the overall success rate was 57.9% (11/19). • Secondary outcome: Clinicians found the CELOX™ PPH easy to use and the average duration of use was 22.2 3 8.1 hrs in the FAS group and 23.0 3 7.14 hrs in the UBPP group.	• There was a significant reduction of 77.8% (OR 4.55, P=0.037, Fisher's Exact Test) in hysterectomies after commencement of CELOX™ PPH • The infection rate for all patients included in this study was 6.9% (7/102) (not related to use of CELOX™ PPH). • There were no CELOX™ PPH -related deaths reported
Dückelmann et al (2019) [Article] (Section 4.3.2)	• CELOX™ PPH (Medtrade) • Balloon tamponade (Cook Medical)	• Retrospective cohort • Patients with PPH • N=78 (CELOX™ PPH, N=47) • Study objective: To compare outcomes in PPH management • Primary outcome: Uterine bleeding termination without additional surgical intervention • Secondary outcomes: Blood loss, number of blood transfusions	• Primary outcome: No significant difference between CELOX™ PPH and Balloon tamponade groups • Secondary outcome: No relevant blood loss in either study group	• PPH-related hysterectomies were reduced by 50% post-introduction of CELOX™ PPH • No patients developed infections • No treatment-associated morbidity • Conclusion: CELOX™ PPH is an excellent treatment for PPH and was at least equivalent to Balloon tamponade
Maul et al (2014) [Poster] (Section 4.3.7)	• CELOX™ PPH (Medtrade)	• Cohort study • Severe PPH • N=35 • Study objective: To describe experience with CELOX™ PPH and to evaluate its effects on maternal outcome	• Study objective: The rate of postpartum hysterectomies was significantly reduced (p=0.011)	• CELOX™ PPH is easy to apply and required no special training • Can be used after both vaginal and caesarean deliveries • Treatment is inexpensive • Conclusion: CELOX™ PPH GAUZE in an option for the treatment of PPH
Maul et al (2015) [Poster] (Section 4.3.6)	• CELOX™ PPH (Medtrade)	• Cohort study • Severe PPH (including cases where postpartum hysterectomy seemed inevitable) • N=65 • Study objective: To compare period before and after introduction of CELOX™ PPH in the treatment of PPH and to evaluate numbers of postpartum hysterectomies	• CELOX™ PPH left in utero for up to 48 hrs • Study objective: The rate of postpartum hysterectomies was significantly reduced (p=0.023)	• No treatment-associated morbidity • CELOX™ PPH treatment is inexpensive compared with other treatments • Conclusion: CELOX™ PPH is an option for the treatment of PPH and significantly reduces postpartum hysterectomies

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Table. Summary of clinical studies for CELOX™ PPH in PPH pt2

Reference	Device (Manufacturer)	Study details	Study results	Additional comments
Schmid et al (2012) [Article] (Section 4.3.11)	• CELOX™ PPH (Medtrade)	• Case report • PPH • N=1 • Study objective: Describe the successful application of CELOX™ PPH in severe case of PPH	• Hemostasis was achieved • After removal of the CELOX™ PPH no subsequent bleeding occurred	• CELOX™ PPH is easy to use and is inexpensive • Conclusion: Application of CELOX™ PPH acts as an effective local hemostat, and is safe as a treatment for PPH
Schmid et al (2013) [Article] (Section 4.3.8)	• CELOX™ PPH (Medtrade)	• Case series • PPH (including cases where postpartum hysterectomy seemed inevitable) • N=19 • Study objective: To describe the use of CELOX™ PPH in the treatment of PPH	• Bleeding stopped immediately after application of CELOX™ PPH and application of compression (1-2 minutes) • Bleeding did not recur • Rate of postpartum hysterectomies was reduced by 75% (p=0.044)	• CELOX™ PPH is easy to apply and required no special training • Can be used after both vaginal and cesarean deliveries • Treatment is inexpensive • No clinical signs of sepsis • In two patients, small fragments of CELOX™ PPH were accidentally left behind and dressing integrity should be routinely checked • No long-term side effects noted • Conclusion: CELOX™ PPH in an option for the treatment of PPH
Seidel et al (2018) [Article] (Section 4.3.10)	• CELOX™ PPH (Medtrade) • Balloon tamponade (Cook Medical)	• Case report • PPH due to uterine atony • N=1 • Study objective: To report a "novel uterine sandwich" approach to treating PPH	• The sandwich technique halted bleeding • No further invasive techniques were required	• Conclusion: Using CELOX™ PPH in combination with balloon tamponade can be useful technique for fertility-preserving management of PPH
von Beckerath et al (2016a) [Poster] (Section 4.3.3)	• CELOX™ PPH (Medtrade) • Balloon tamponade (Cook Medical)	• Unblinded, randomised, parallel and prospective study • Atonic PPH • N=61 (CELOX™ PPH, N=31) • Study objective: Effectiveness of intrauterine insertion of CELOX™ PPH compared to use of Balloon tamponade • Primary outcome: Need for further surgical intervention (e.g., hysterectomy) • Secondary outcome: fever, admission ICU	• Primary outcome: Failure rate leading to peripartum hysterectomy 9.7% in CELOX™ PPH group vs. 40.0% in Balloon tamponade group • Secondary outcome: low grade fever slightly higher in CELOX™ PPH group; admission to ICU similar in both groups	• CELOX™ PPH is inexpensive, easy to use and has manageable side effects compared with Balloon tamponade method • Conclusion: CELOX™ PPH a potentially effective method in the management of atonic PPH
von Beckerath et al (2016b) [Poster] (Section 4.3.5)	• CELOX™ PPH (Medtrade)	• Multicentre study • PPH • N=98 • Study objective: Report any side effects of CELOX™ PPH and any reduction in postpartum hysterectomies	• Study objective: After introduction of CELOX™ PPH the rate of postpartum hysterectomies was significantly reduced (0.05% vs. 0.18%, p=0.018) • increase in inflammation levels (CRP and leukocytes) in blood	• CELOX™ PPH is easy to apply and is cost effective • Conclusion: CELOX™ PPH can be used in the treatment of PPH. No major adverse events reported. CELOX™ PPH reduces number of postpartum hysterectomies

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4.3.1. Retrospective analysis study (n=102) on the use of CELOX™ PPH as a treatment for PPH compared with current standard of care.

Postpartum Haemorrhage:
CELOX™ PPH retrospective data analysis report (Charité data).
Henrich, W, Dückelmann A, Giroud D, Sarr Y. Version 1.1 – 19 May 2022.
Retrospective analysis study (n=102)

- Assessment of 102 patients with PPH who did not respond to conventional treatments
- Primary objective: to control uterine bleeding in PPH with CELOX™ PPH
- CELOX™ PPH demonstrated 100% successful haemostasis in all patients with grade 1 and 2 bleeds (up to 2500mls) for all deliveries
- CELOX™ PPH demonstrated 95.7% successful haemostasis in all patients with grade 1 to 3 bleeds (up to 8000mls) for vaginal deliveries
- Following the introduction of CELOX™ PPH the incidence of hysterectomies was significantly reduced (versus standard of care) by 77.8%

In a retrospective evaluation undertaken in the Department of Obstetrics and Gynecology at the University Hospital Charité, Berlin, 102 patients, whose PPH (uterine, vaginal, or cervical) did no respond to conventional treatments, were assessed for the control of uterine bleeding in PPH using CELOX™ PPH. The primary objective of the study was to evaluate the effectiveness of CELOX™ PPH in controlling uterine bleeding for primary PPH. The primary performance endpoint (outcome) was the proportion of patient-controlled bleeding in less than five minutes (indicating a successful outcome). Secondary outcomes included safety (e.g. adverse events particularly related to the need for additional interventions, infection rate, allergic response), and performance (e.g., ease of application, duration of application). An analysis of patients with a clear indication of uterine haemorrhage (n=91), CELOX™ PPH was effective in halting blood loss in 91.2% (83/91) (CI 85.4%, 97.0%) patients (Appendix 1, Table 9). In relation to the delivery path, 58.2% (53/91) had a vaginal delivery and 94.3% (50/53) reached successful haemostasis with CELOX™ PPH, whereas only 5.7% (3/53) patients experienced unsuccessful haemostasis with CELOX™ PPH. (Appendix 1, Table 10). Thirty-eight (41.8%) patients with uterine PPH required a caesarean section, of which 86.8% (33/38) reached successful haemostasis with CELOX™ PPH, whereas 13.2% (5/38), encountered unsuccessful haemostasis with CELOX™ PPH.

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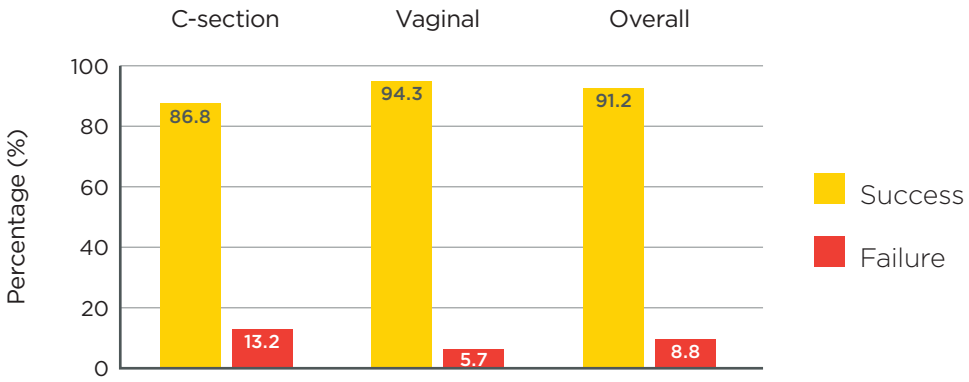
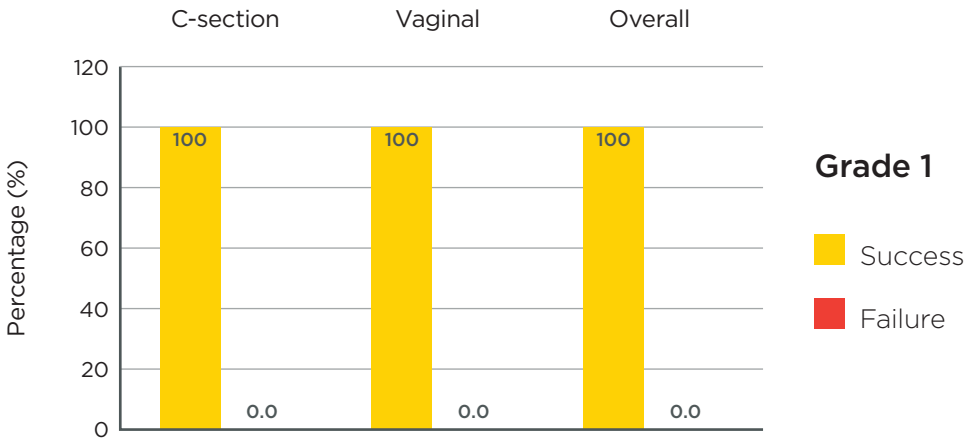
Figure 10. Success/failure of CELOX™ PPH haemostasis by delivery mode in patients with uterine PPH



Three different grades of PPH (grades 1, 2, and 3) were defined according to a number of different parameters, including quantity of blood loss. Of the 91 patients, 23.1% (21/91) had grade 1 (reported blood loss 800-1000ml), 56.0% (51/91) grade 2 (1200-2500ml), and 20.9% (19/91) had grade 3 (2600-8000ml). CELOX™ PPH reached 100% successful haemostasis in all patients with grades 1 and 2. For grade 3, the overall success rate was 57.9% (11/19) (Figure 11).

Figure 11. Success/failure of CELOX™ PPH haemostasis by delivery mode based on grades of PPH



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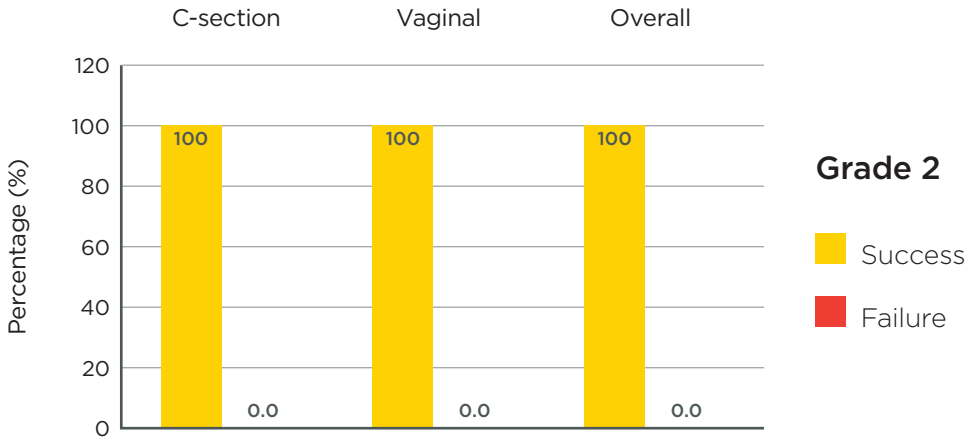

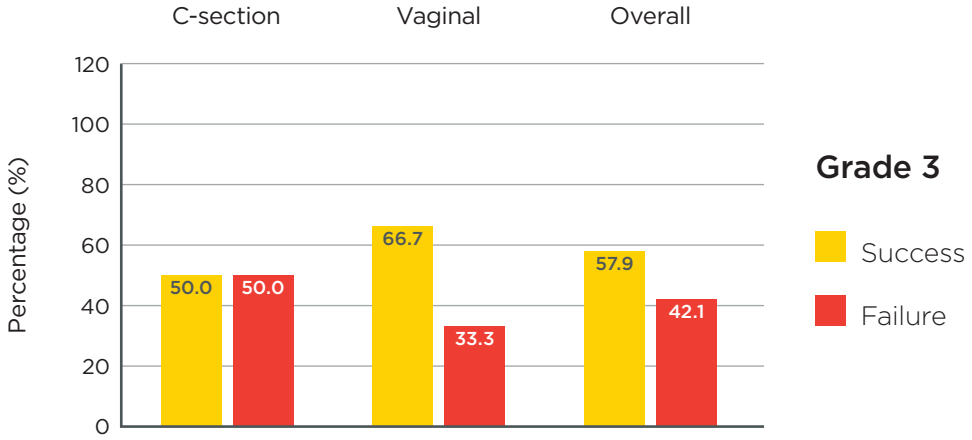

There were no device-related events except for one possible procedure-related event where it was reported that during insertion a possible damage to the uterotomy suture of the caesarean section occurred. The overall occurrence rate of safety events appears to be slightly lower compared to Bakri balloon (Appendix 1, Tables 10 and 11). The infection rate for all patients included in this study was 6.9% (7/102), but no infections were attributable solely and directly to CELOX™ PPH. After the introduction of CELOX™ PPH, the incidence of hysterectomy over a span of 31 months was remarkably low, with only two cases out of 9,167 births necessitating hysterectomy. In the 31 months preceding the implementation of CELOX™ PPH, a total of nine hysterectomies were performed out of 9,058 births. This is a significant reduction of 77.8% (OR 4.55, P=0.037, Fisher's Exact Test). Five new pregnancies successfully brought to term with healthy babies are to be reported among the patients studied in this retrospective analysis. There were no problems reported with insertion or removal of CELOX™ PPH (Appendix 1, Table 12).

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4.3.2. Retrospective cohort study (n=78) comparing outcomes in PPH management using CELOX™ PPH versus balloon tamponade.

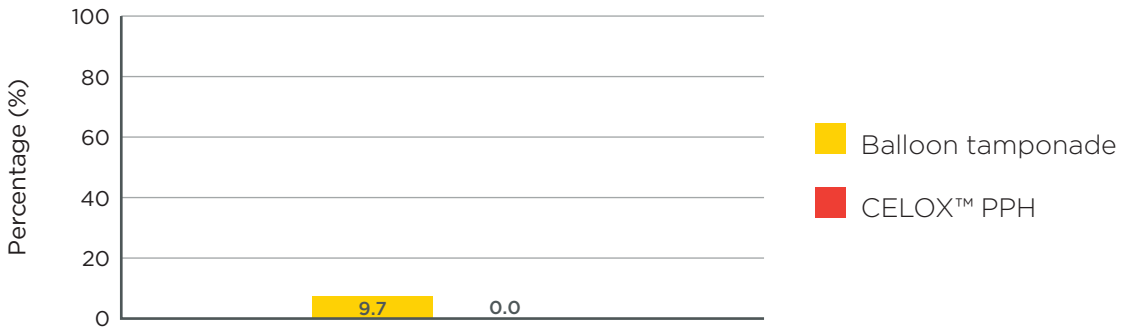
Uterine packing with CELOX™ PPH compared to balloon tamponade for managing postpartum haemorrhage.

Dueckelmann AM, Hinkson L, Nonnenmacher A, Siedentopf JP, Schoenborn I, Weizsaecker K, Kaufner L, Henrich W, Braun T. Eur J Obstet Gynecol Reprod Biol. 2019; 240:151-155.

Retrospective cohort study (n=78)

- Assessment of the effectiveness and safety of CELOX™ PPH versus balloon tamponade for managing severe PPH
- CELOX™ PPH is an excellent treatment for severe PPH and is at least equivalent to the balloon tamponade
- Following the introduction of CELOX™ PPH the incidence of hysterectomies (versus standard of care) was reduced by 50%
- CELOX™ PPH is particularly effective in managing PPH resulting from uterine atony or placenta bed bleeding following vaginal or caesarean section deliveries.
- CELOX™ PPH is especially beneficial for cases involving lower uterine segment atony, placenta previa bed bleeding, and coagulopathy.
- No adverse events or treatment-related morbidity were linked to CELOX™ PPH

In a retrospective cohort study evaluation set in a university hospital obstetrics department, seventy-eight patients (47 received CELOX™ PPH, thirty-one received balloon tamponade (Bakri Balloon)). The primary objective of the study was to compare the outcomes in management of PPH. The primary outcome of the evaluation was uterine bleeding termination without additional surgical intervention. Secondary outcomes included blood loss, and number of blood transfusions (Dueckelmann et al, 2019). CELOX™ PPH was as effective as balloon tamponade in halting uterine bleeding, or blood loss. Three patients in the balloon tamponade group required a hysterectomy. No hysterectomy was required in the CELOX™ PPH group. During an observation period of 18 months before (5414 deliveries) and 18 months (5430 deliveries) after introduction of CELOX™ PPH at one clinic location four and two, respectively, PPH-related hysterectomies had to be performed. Thus, the rate of peripartum hysterectomies was reduced by 50%. The authors concluded that CELOX™ PPH is an excellent treatment for PPH and appeared to be at least equivalent to the balloon tamponade for treating severe PPH (Appendix 1, Table 13).



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4.3.3. Randomised, prospective evaluation (n=61) comparing the effectiveness of CELOX™ PPH with balloon tamponade in patients with PPH.

Comparison of CELOX™ PPH and Bakri balloon in management of primary atonic postpartum Haemorrhage.

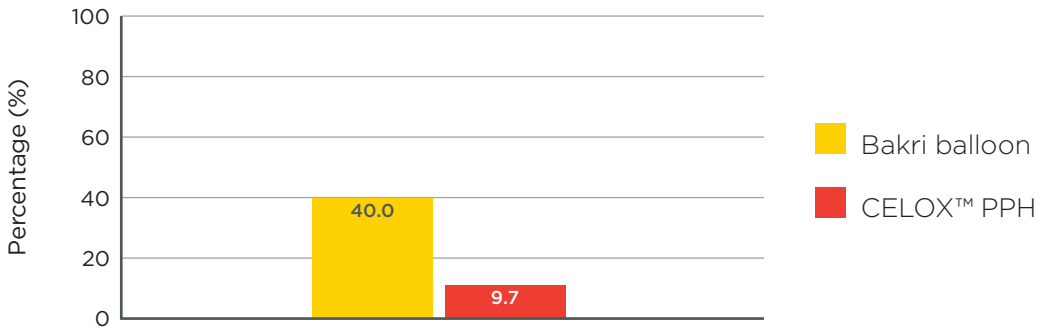
Von Beckerath AK, Maul H, Elmohandes AM, Shaaban M, Habib DM, Nasr A, Abdel-Kawi AF. Am J Obstet Gynecol. 2016; 214(1 Suppl 1):S335. [poster presentation]

Randomised, prospective study (n=61)

- Assessment of the effectiveness of intrauterine insertion of CELOX™ PPH in comparison to Bakri balloon
- Failure rate which led to peripartum hysterectomies were 9.7% (3/31) in the CELOX™ PPH group compared to 40% (12/30) in the Bakri balloon group
- CELOX™ PPH is a potentially effective treatment in the management of atonic PPH
- CELOX™ PPH is cost effective, and is easy to use compared to the standard balloon therapy

The effectiveness of CELOX™ PPH to control PPH was assessed in an unblinded, randomised, parallel prospective study in sixty-one patients with atonic PPH. Thirty-one patients received CELOX™ PPH, and 30 patients were treated with Bakri balloon (von Beckerath et al, 2016a). Three patients receiving CELOX™ PPH required postpartum hysterectomy which equated to a 9.7% failure rate. This compared to a failure rate of 40.0% (12/30) in the Bakri balloon group (Figure 12).

Figure 12. Failure rate leading to hysterectomy



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4.3.4. Historical, retrospective cohort study evaluation (n=666) comparing the effectiveness of CELOX™ PPH with balloon tamponade or medical therapy in patients with PPH.

Does the use of CELOX™ PPH for postpartum haemorrhage reduce the need for surgical therapy including hysterectomy? A databased historical cohort study.

Biele C, Radtke L, Kaufner L, Hinkson L, Braun T, Henrich W, Dückelmann AM. J Perinat Med. 2022; 50(8):1078-1086.

Retrospective cohort study (n=666)

- Assessment of the effectiveness of CELOX™ PPH in comparison with balloon tamponade, and medical therapy only
- Groups were compared in terms of therapy success, side-effects, and the primary outcome was the need for surgical measures (e.g., hysterectomy)
- No significant differences in the need for surgical therapy between groups.
- CELOX™ PPH group had significantly fewer hysterectomies compared to the balloon tamponade group.
- Following the introduction of CELOX™ PPH, the incidence of PPH-related hysterectomies was significantly reduced by 77.8%.
- No adverse events related to CELOX™ PPH
- CELOX™ PPH is easy to use and cost-effective compared to alternative devices.

Biele and colleagues (2022) reported a database-based, retrospective case-control study evaluation (n=666) comparing CELOX™ PPH with that of balloon tamponade and medical therapy (the use of uterogenic and/or haemostatic drugs) only. A total of 530 received medical therapy only, 51 balloon tamponade, and 85 CELOX™ PPH. The primary outcome of the study was the need for further surgical/radiological therapies (e.g., compressing sutures, selective devascularisation, (re-)laparotomy and hysterectomy). The secondary outcomes included duration of inpatient stay, admission to ICU, and inflammatory markers. There was no significant difference in the need for surgical therapy, but a significantly lower number of hysterectomies in the CELOX™ PPH group compared to the balloon tamponade group was reported (Figure 13). There were no significant differences in secondary outcomes and no adverse events related to CELOX™ PPH. Since the introduction of CELOX™ PPH, the number of PPH-related hysterectomies reduced significantly by 77.8% (7.8% vs. 0.0%, p=0.018) (Figure 15).

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Figure 13. Hysterectomies due to PPH before and after the introduction of CELOX™ PPH

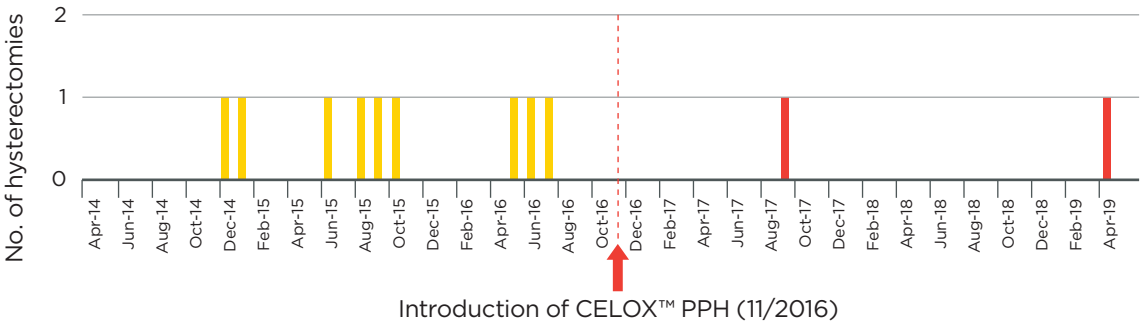
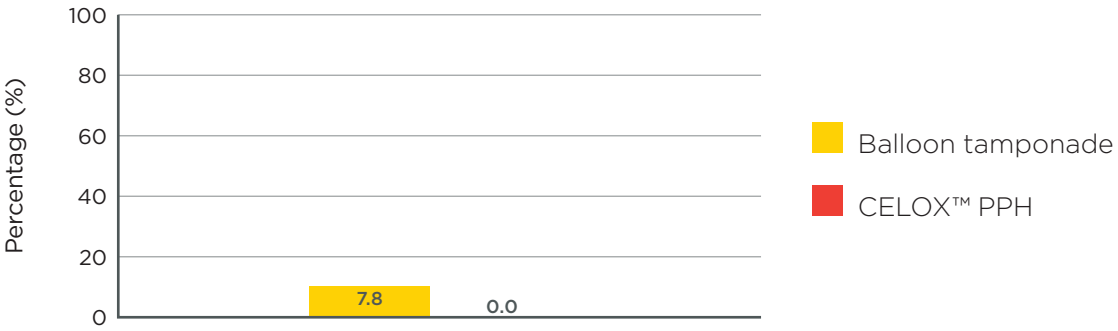


Figure 14. Percentage of patients requiring hysterectomy



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4.3.5. Clinical evaluation (n=98) of CELOX™ PPH in patients with PPH.

Use of CELOX™ PPH in 98 cases of severe postpartum haemorrhage–a multicenter registry analysis.

Von Beckerath AK, Maul H, Gebauer G, Abdel-Kawi AF, Rolf N, Saade G, Bader W, Kusnierczak D, Berger R, Kienast C, Kienemund J, Schmid B. Am J Obstet Gynecol. 2016; 214(1 Suppl 1):S269. [poster presentation]

Multicentre registry analysis study (n=98)

- Assessment of the potential side effects of CELOX™ PPH, and to assess if the use of CELOX™ PPH reduces the rate of postpartum hysterectomies
- Women with PPH were treated in accordance to guidelines with the addition of uterine packing using CELOX™ PPH
- After the introduction of CELOX™ PPH the rate of postpartum hysterectomies reduced from 0.18% to 0.05% (p=0.0183)
- No adverse events were observed or reported
- CELOX™ PPH is cost-effective and easy to use

The study examined the effectiveness of CELOX™ PPH in managing persistent bleeding PPH cases, involving ninety-eight women, where standard medical uterotonic interventions had failed. The objective of the multicentre CELOX™ PPH registry analysis was to report on potential side effects of CELOX™ PPH and to assess if the use of CELOX™ PPH reduced the rate of postpartum hysterectomies (von Beckerath et al, 2016b). After the introduction of CELOX™ PPH the rate of postpartum hysterectomy was significantly reduced (0.05% vs. 0.18%, p=0.018) (Figure 14). Two patients experienced uncomplicated pregnancies following treatment with CELOX™ PPH, and there were no instances of maternal mortality after the introduction of this medical intervention. Elevated levels of C-reactive protein (CRP) and leukocytes (WBC) were observed in patients who received CELOX™ PPH. Approximately 10% of patients developed a fever; however, none displayed any indications of sepsis. Please note that the gauzes were removed 24 hours after insertion, with a permissible window of up to 6 additional hours*.

*CELOX PPH is approved and indicated for use with a maximum insertion time of up to 24 hours

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Figure 16. Rate of hysterectomy before and after introduction of CELOX™ PPH

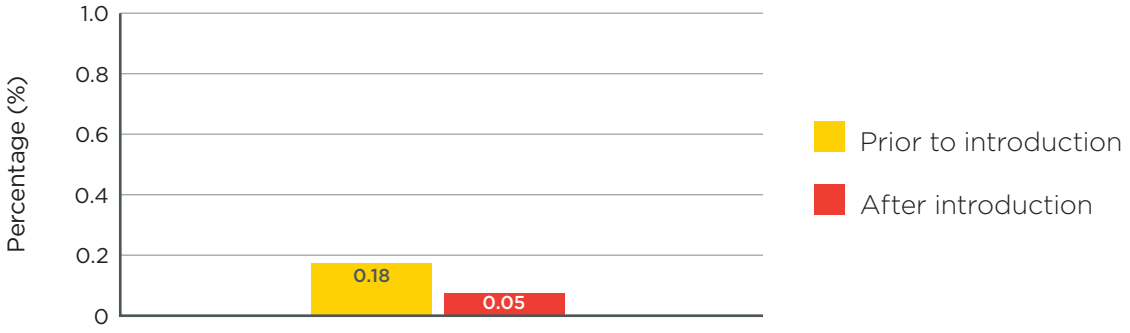
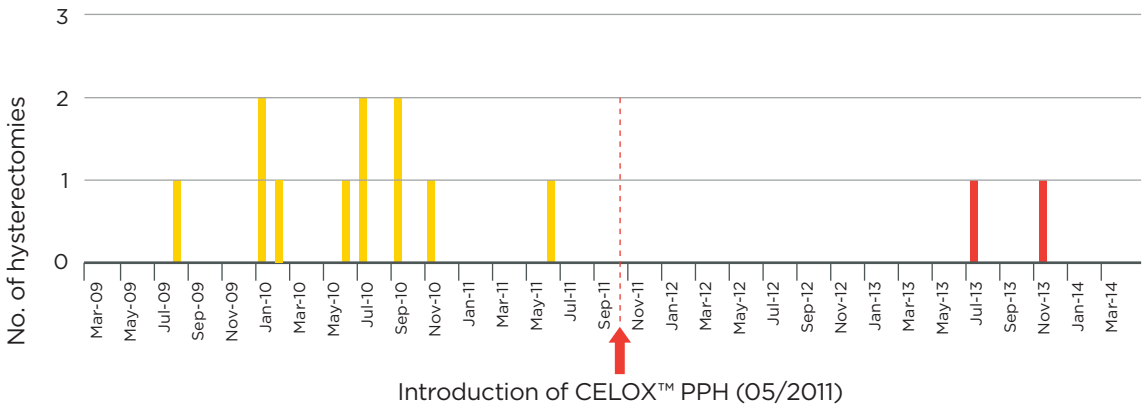


Figure 14. Hysterectomies due to PPH before and after the introduction of CELOX™ PPH



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4.3.6. Clinical evaluation (n=65) of CELOX™ PPH in patients with severe PPH (including cases where risk of postpartum hysterectomy is high).

Uterine packing with CELOX™ PPH for control of postpartum Haemorrhage (PPH).

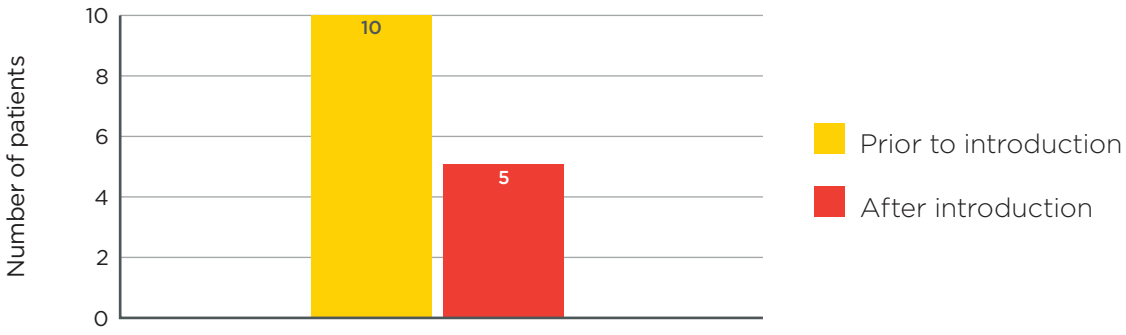
Maul H, Steinmacher S, Saade G, Gebauer G, Rolf N, Schmid B. Am J Obstet Gynecol. 2015; 212(1 Suppl 1):S358-S359. [poster presentation]

Case study series (n=65)

- Objective: to compare a 26 month period before and a 38 month period after the introduction of CELOX™ PPH in the treatment of PPH
- Women with PPH were treated by uterine packing with CELOX™ PPH through the hysterotomy in caesarean delivery, or transvaginally
- CELOX™ PPH is a viable option in the treatment of PPH
- After the introduction of CELOX™ PPH postpartum hysterectomies were significantly reduced (p=0.023)
- CELOX™ PPH can be safely used after both vaginal and caesarean section
- No complications related to CELOX™ PPH treatment were observed
- The use of CELOX™ PPH is inexpensive

In a cohort study of patients suffering from severe PPH, sixty-five women were treated with uterine packing with CELOX™ PPH via the hysterotomy in caesarean delivery, or transvaginally. 15036 consecutive births before and after the introduction of CELOX™ PPH (n=5498 vs. n=9538 deliveries) were analysed. The objective of the study was to compare the postpartum hysterectomies before and after the introduction of CELOX™ PPH (Maul et al, 2015). Compared with 26 months before, in the 38 months after introduction of CELOX™ PPH, the rate of postpartum hysterectomies was significantly reduced (10 vs. 5, p=0.023) (Figure 15). CELOX™ PPH was left in utero for up to 48 hours* (mean 20.63 hours). Maternal mortality after the introduction of CELOX™ PPH was zero.

Figure 15. Number of postpartum hysterectomies before and after introduction of CELOX™ PPH



*CELOX PPH is approved and indicated for use with a maximum insertion time of up to 24 hours

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4.3.7. Clinical evaluation (n=35) of chitosan-covered (CELOX™ PPH) gauze in patients with PPH.

Uterine packing with CELOX™ PPH for control of postpartum Haemorrhage.

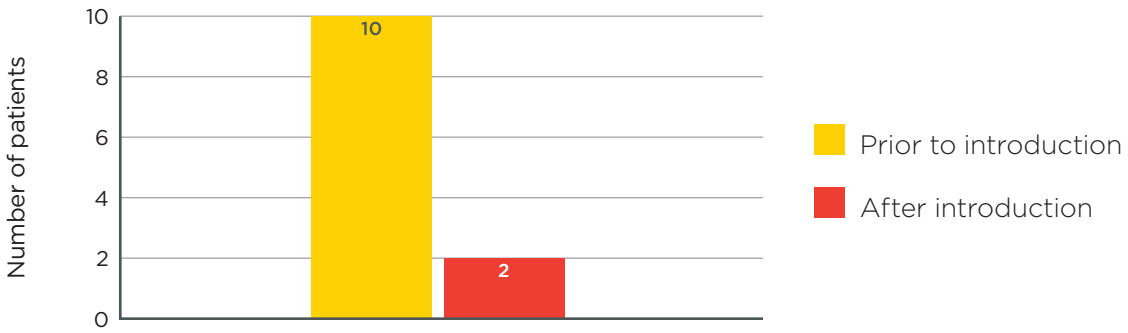
Maul H, Gebauer G, Rolf N, Saade G, Rezniczek G, Schmid B. Am J Obstet Gynecol. 2014; 210(1 Suppl 1):S281-S282. [poster presentation]

Case study series (n=35)

- Objective: to describe 26 months of experience using CELOX™ PPH in the treatment of PPH
- Over comparable periods of time (26 months) and similar number of births (n=5498 vs. n=6222) before and after the introduction of CELOX™ PPH there was a significant reduction in the rate of postpartum hysterectomies (p=0.011)
- CELOX™ PPH is a viable option for the treatment of (severe) PPH
- CELOX™ PPH is easy to apply and can be used after both vaginal and caesarean deliveries and requires no special training
- CELOX™ PPH is inexpensive compared to other treatment options
- No complications related to CELOX™ PPH treatment were observed

CELOX™ PPH was used in the control of severe PPH and was reported in a cohort study evaluation of thirty-five cases of PPH (Maul et al, 2014). Over comparable periods of time (26 months) and births (n=5498 vs. CELOX™ PPH, the rate of peripartum hysterectomies was significantly reduced (10 vs. 2, p=0.011) (Figure 16). Clinicians reported that no postpartum hysterectomies had been performed for 23 months since the introduction of CELOX™ PPH.

Figure 16. Number of postpartum hysterectomies before and after introduction of CELOX™ PPH



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4.3.8. Case studies: use of CELOX™ PPH in patients (n=19) with severe PPH (including cases where risk of postpartum hysterectomy is high).

Uterine packing with CELOX™ PPH for control of postpartum Haemorrhage.

Schmid BC, Rezniczek GA, Rolf N, Saade G, Gebauer G, Maul H.. Am J Obstet Gynecol. 2013; 209(3):225.e1-225.e5.

Case study series (n=19)

- Assessment of the use of CELOX™ PPH in the treatment of PPH
- Women with PPH were treated with uterine packing using CELOX™ PPH either through the hysterotomy, in the case of caesarean delivery or transvaginally
- In all but one case (18/19) bleeding was halted and no further intervention was required
- Over equivalent 18-month periods and with a comparable number of births (3822 vs. 4077) before and after the introduction of CELOX™ PPH, the rate of peripartum hysterectomies was reduced by 75% (p = .044)

Schmid and colleagues (2013) reported their experience of using CELOX™ PPH in 19 patients with PPH including several cases (n=5) where postpartum hysterectomy seemed inevitable. Patients suffering from PPH were treated by uterine packing with CELOX™ PPH, either through the hysterotomy in case of caesarean delivery or transvaginally, for up to 24 hours. In all but one case, the bleeding stopped, and further interventions were avoided. Bleeding stopped immediately (1-2 minutes) after application of CELOX™ PPH, and application of compression and bleeding did not recur. The clinicians reported that over comparable periods of time (18 months) and births (3822 vs. 4077) before and after the introduction of CELOX™ PPH in their clinic, the rate of peripartum hysterectomies was reduced by 75% (8 vs. 2, P=0.044) (Figures 17 and 18). CELOX™ PPH was found to be easy to use and required no special training. No adverse effects were reported. In two patients, small fragments of CELOX™ PPH were accidentally left behind and it is recommended that dressing integrity should be routinely checked.

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Figure 17. Number of postpartum hysterectomies before and after introduction of CELOX™ PPH

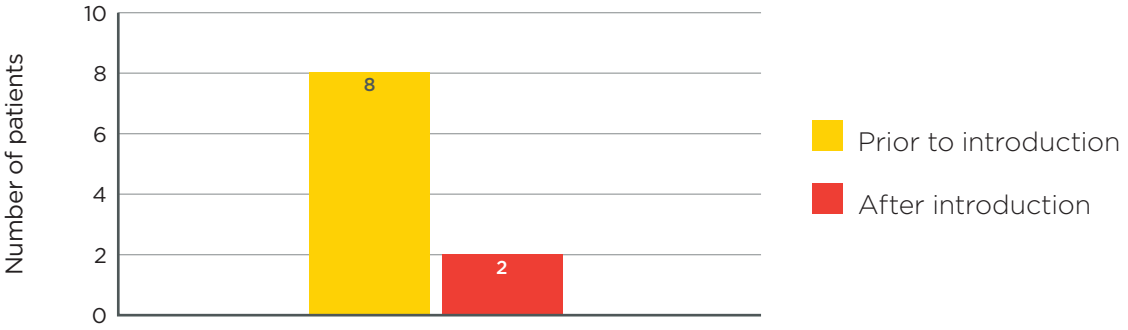
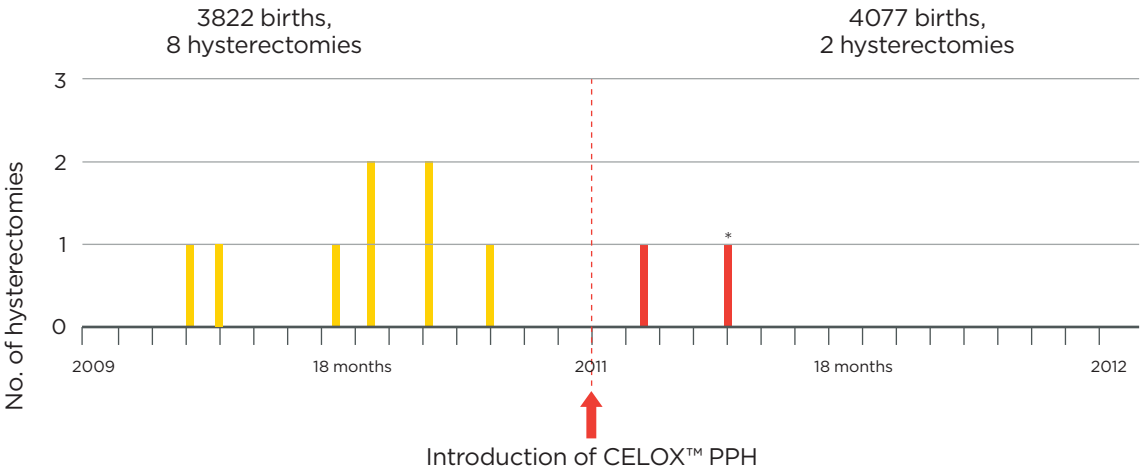


Figure 18. Hysterectomies before and after introduction of CELOX™ PPH



*CELOX™ PPH Gauze not used

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4.3.9. Case studies: use of CELOX™ PPH in patients with (n=4) life-threatening obstetric bleeding.

Uses of CELOX™ PPH for treating different forms of serious obstetrics haemorrhages.

Carles G, Dabiri C, Mchirgui A, Saoudi EO, Hcini N, Pouget K, Seve B, de Matteis B. J Gynecol Obstet Hum Reprod. 2017; 46(9):693-695.

Case study series (n=4)

- Four cases where CELOX™ PPH was used to treat severe obstetric haemorrhage
- Two chitosan variants, in powder and CELOX™ PPH form, were used*
- In all four cases, chitosan effectively resolved the severe obstetric haemorrhage
- Treatment with CELOX PPH was inexpensive, and required no training

Carles et al (2017) reported the application of CELOX™ PPH or chitosan powder* to treat life-threatening obstetric bleeding. Two cases of significant obstetric bleeding treated with the application of CELOX™ PPH were described. In the first case, a 35-year-old woman in her 10th pregnancy presented at the emergency room in early labour. After an emergency caesarean delivery, the patient displayed extensive bleeding and haemodynamic instability. Despite transfusions, haemodynamic sutures, and compression of the pelvis the patient continued to bleed from the edge of the cervix and within the pelvic cavity. Upon packing of the pelvic cavity with CELOX™ PPH the bleeding stopped completely within five minutes of application. CELOX™ PPH was removed, without difficulty, during surgery two days later**. In a second case, a 25-year-old woman presented with spontaneous labour at 40 weeks. The labor proceeded without complications, resulting in spontaneous delivery of the baby, facilitated by the administration of a 10 IU of oxytocin via intravenous injection. The patient then displayed abnormal bleeding, but no abnormalities were found upon examination. Despite administration of an additional 10 IU of oxytocin via intravenous injection and a one-hour intravenous infusion of a sulprostone ampoule, blood loss continued, and it was decided to pack the uterus with CELOX™ PPH. Bleeding stopped immediately upon application of the gauze. CELOX™ PPH was removed the day after delivery, by simply pulling it out of the uterine cavity. Another case involved a patient in late pregnancy with preeclampsia. As her preeclampsia worsened during labor, she received a combination of urapidil and magnesium sulfate. Vacuum extraction was performed due to abnormal fetal heart rate during the second stage of labor. An intravenous injection of 5 IU

*CELOX™ PPH gauze is the only product approved for use in cases of uterine PPH
**CELOX PPH is approved and indicated for use with a maximum insertion time of up to 24 hours

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oxytocin aided delivery, and though the placenta initially appeared complete, the patient experienced significant postpartum bleeding, estimated at over 2 liters of blood loss. Examination revealed extensive, bleeding vaginal tears that resisted traditional haemostatic measures. Chitosan powder* application and gauze compression for five minutes effectively stopped the bleeding. There was no further vaginal bleeding, and haemostatic tests returned to normal within two days.

4.3.10. Case report: use of CELOX™ PPH in combination with balloon tamponade for management of PPH.

Application of CELOX™ PPH in combination with intrauterine balloon tamponade for postpartum Haemorrhage treatment – Case report of a novel "uterine sandwich" approach.

Seidel V, Braun T, Weizsäcker K, Henrich W. Int J Surg Case Rep. 2018; 48:101-103.

Case report (n=1)

- Presentation of a case of PPH where a novel "uterine sandwich" (a combination of CELOX™ PPH and intrauterine balloon tamponade) used to halt blood loss
- The novel treatment strategy was effective at stopping further blood loss
- The use of the "uterine sandwich" prevented the need for more invasive second stage intervention

CELOX™ PPH has been used in a patient with PPH using a "uterine sandwich" approach using a combination of CELOX™ PPH with an intrauterine balloon tamponade to prevent blood loss (Seidel et al, 2018). At about 35 weeks a planned caesarean section delivered three healthy boys. However, within 2.5 hours the uterus became atonic and filled with blood. As it was the first pregnancy for the woman, a fertility preserving strategy was preferred. CELOX™ PPH was inserted, and an intrauterine balloon tamponade was added to the uterus. Bleeding was stopped after the additional insertion of the balloon. No further surgical intervention was necessary.

*CELOX™ PPH gauze is the only product approved for use in cases of uterine PPH

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4.3.11. Case report: use of CELOX™ PPH in a severe case of PPH.

Postpartum Haemorrhage: use of CELOX™ PPH.

Schmid BC, Rezniczek GA, Rolf N, Maul H. Am J Obstet Gynecol. 2012; 206(1):e12-e13.

Case report (n=1)

- Reporting of a case of PPH where conservative treatment proved ineffective, and CELOX™ PPH was used
- Tight uterovaginal packing with CELOX™ PPH was performed in an effort to arrest recurring haemorrhage
- CELOX™ PPH achieved haemostasis and remained in place for 36 hours*
- By achieving haemostasis, CELOX™ PPH prevented a seemingly inevitable hysterectomy
- The ease of application and cost-effectiveness of CELOX™ PPH present a promising addition to the treatment options for PPH

The use of CELOX™ PPH for the control of severe PPH has been described in the case of a 32-year-old woman who underwent an elective caesarean section delivery and where conservative interventions to control uterine bleeding had failed (Schmid et al, 2012). Oxytocin administration initially achieved haemostasis on two occasions, but subsequent bleeding occurred. Curettage revealed no retained placental tissue, and the clinical picture was compatible with uterine atony. As control of bleeding had not been achieved the decision was taken to perform tight uterovaginal packing with CELOX™ PPH. The clinicians noted that a hysterectomy was the only remaining alternative. Application of CELOX™ PPH resulted in haemostasis, and the gauze was left in place for 36 hours*. After removal of the CELOX™ PPH, no more bleeding occurred.

*CELOX PPH is approved and indicated for use with a maximum insertion time of up to 24 hours

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5. COST-EFFECTIVENESS OF CHITOSAN-DERIVED HAEMOSTATIC DRESSINGS

Section key points

- Significant costs are associated with bleeding, particularly in cases of PPH
- Any clinical intervention that reduces the bleeding, as well as the need for associated clinical procedures (e.g., surgery) have the potential to provide cost efficiencies
- CELOX™ PPH could provide cost-saving benefits
- Uncontrolled bleeding in the surgical and trauma settings results in a significant clinical and economic impact and achieving haemostasis is a crucial focus for clinicians (Schreiber and Neveleff, 2011)

5.1. The cost of bleeding following surgical procedures

Bleeding is a common complication in surgical procedures and ranges in extent from mild/moderate to severe/traumatic/disruptive and may occur intra- or post-operatively (Ghadimi et al, 2016). A considerable portion of bleeding complications is observed among surgical patients post-surgery. A recent large retrospective analysis identified almost 30% bleeding related complications. Other data suggests bleeding rates ranging from <10% to 35% (Marietta et al, 2006). Cardiac procedures have some of the highest risks of bleeding, with almost 50% of patients experiencing some bleeding-related complication (Shander, 2007). Uncontrolled bleeding is associated with increased risk of mortality, necessitating blood transfusions and leading to increased healthcare costs due to increased resource utilisation (Stokes et al, 2011). Managing complications arising from uncontrolled bleeding may involve several additional clinical procedures, including:

1. Prolonging the duration of the initial surgical procedure.
2. The need for transfusion of whole blood, plasma, and/or plasma substitutes.
3. The use of hemostatic agents.
4. Re-operative surgery.
5. Extension of the hospital stay.

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In addition to the health consequences associated with bleeding, such as increased morbidity and mortality, there will also be a corresponding increase in costs due to the additional utilisation of hospital resources as outlined above (Zimmerman, 2007; Boucher and Traub, 2009).

5.2. Anti-coagulated patients – risks and associated costs

Excessive bleeding is a frequent complication in surgical procedures (Ghadimi et al, 2016). When patients are undergoing anticoagulant therapy, such as warfarin or heparin, this further complicates surgical interventions and heightens the associated risk. The use of anticoagulants increases the probability of excessive or uncontrolled bleeding during surgery.

Anticoagulation therapy is occasionally required during pregnancy or the postpartum period for women with a high risk of deep vein thrombosis (VTE), prior venous thromboembolism, prosthetic heart valves, atrial fibrillation, left ventricular dysfunction, or a history of fetal loss.

The use of anticoagulants during pregnancy is intricate due to the potential teratogenic effects and dosing complexities associated with these agents. Managing anticoagulation around the time of labor is further complicated by the heightened risk of bleeding. Furthermore, women receiving chronic anticoagulation who are considering pregnancy require counseling on minimising the risk of warfarin-related teratogenic effects and the passage of anticoagulants to the fetus.

Low molecular weight heparin (LMWH) is the favored anticoagulant for pregnant women due to its placenta-impermeable nature, enhancing fetal safety. Nevertheless, some women, especially those with mechanical heart valves, may necessitate vitamin K antagonists (VKAs) as LMWH may not suffice. Anticoagulation therapy during pregnancy entails a risk of bleeding, warranting close monitoring throughout (Bauer, 2023).

5.3. Costs associated with maternal morbidity

Maternal morbidity encompasses multiple physical and psychological health conditions that result from or are aggravated by pregnancy. These conditions can start during pregnancy or within the first year postpartum.

A recent review of societal cost of nine selected maternal morbidities in the United States was undertaken. The results demonstrated that using the prevalence estimates for each of the nine conditions included in our model, aggregated costs associated with each condition for all pregnancies or live births in 2019 to estimate a total cost of $32.3 billion from conception to five years postpartum. Of the total cost, the estimates were $18.7 billion in medical costs and $13.6 billion in nonmedical costs. Two-thirds of these costs occurred within the first year postpartum. Maternal mental health conditions ($18.1 billion), hypertensive disorders ($7.5 billion), gestational diabetes mellitus ($4.8

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billion), and haemorrhage ($1.8 billion) generated the largest costs (Appendix 1, Table 14). This underscores the importance of addressing these maternal morbidities comprehensively, not only from a healthcare perspective but also from an economic standpoint, in order to improve maternal and child health outcomes while managing healthcare costs.

5.4. Costs associated with treating PPH

5.4.1. Overall costs of treating PPH

There have been limited studies examining the costs associated with obstetric bleeding. For example, a study conducted by the University of California, Los Angeles (UCLA) Center for Health Policy Research, focusing on the costs of maternal hemorrhage in California (Pourat et al, 2013), demonstrated the following:

- Approximately 4.6% (22,730) of births in California in 2011 were complicated by maternal hemorrhage.
- The average cost of an uncomplicated delivery in 2011, encompassing both maternal and neonatal expenses for both vaginal and caesarean deliveries, was estimated at $5,000. Specifically, an uncomplicated delivery with a healthy neonate cost around $4,500 for vaginal births and $6,500 for caesarean births.
- The total estimated additional cost associated with maternal hemorrhage deliveries reached $105,956,000.
- The total incremental costs of maternal haemorrhage has been shown to be higher when antepartum haemorrhage is a complicating condition. The incremental cost of a scheduled caesarean with antepartum and postpartum haemorrhage is estimated at $89,300, compared to $3,000 without antepartum haemorrhage.

These findings highlight the significant financial implications of maternal haemorrhage, underlining the importance of further research and healthcare strategies to address and mitigate the economic burden associated with obstetric bleeding.

5.4.2. Cost effectiveness of medical device treatment of PPH

In cases where patients do not respond to uterotonic drugs or surgical interventions, the introduction of uterine balloon tamponade (UBT) devices has proven successful (Suarez et al, 2020). Several authors have reported that the use of a UBT device offers a practical and cost-effective means of managing uncontrolled PPH. This is particularly relevant in scenarios where uterotonic drugs are ineffective or unavailable, or when surgical options are not accessible (Herrick et al. in 2017 and Finlayson et al. in 2021).

However, it's essential to highlight that the field of obstetrics has seen limited innovation, resulting in the dominance of UBTs as the primary medical device for PPH treatment for many years. Consequently, this has sparked an increasing need for more cost-effective alternatives, such as CELOX™ PPH.

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5.5. Cost effectiveness of CELOX™ PPH

There is currently a lack of cost-effectiveness evidence regarding the use of CELOX™ PPH for treatment of PPH. However, a pragmatic way to gauge its potential cost-effectiveness is to examine its positive impact on PPH treatment and make informed assumptions. For a comprehensive overview, please refer to Table 15 (Appendix 1), which summarises the various complications related to PPH, the treatments associated with those complications, their respective costs, and how CELOX™ PPH contributes to favorable outcomes.

Complication	Treatment	Associated cost	Positive impact	Cost reduction
Anaemia	Transfusion	Europe: transfusion of two units of blood – €877.69 (Abraham and Sun, 2012) USA: transfusion of one unit of blood – range $900-$3,500 (https://www.thepricer.org/blood-transfusion-cost/)	Reduce blood loss and need for transfusion (Hatamabadi et al, 2015, Carles et al, 2017, Henrich et al, 2023)	Yes
Hypovolemic shock	Transfusion		Reduce blood loss and need for transfusion	Yes
Coagulation disorders	Transfusion, blood product		Stimulation of haemostasis (Pozza et al, 2011, Hatamabadi et al, 2015, Millner et al, 2009)	Yes
Hysterectomy	Surgery	UK: peripartum hysterectomy, mean adjusted additional cost: £5,380 (Achana et al, 2017) US: laparoscopic and vaginal costs $11,637 and $12,229, respectively (Kohn et al, 2022)	A hysterectomy with persistent bleeding was treated through pelvic packing with CELOX™ PPH that stopped bleeding (Carles et al, 2017)	Yes
Infection/ sepsis	Medical treatments, extended hospital stays, ICU care, surgical procedures, medications, diagnostic tests, and follow-up care	Mean total hospital costs per patient (globally), range €1,101 – €91,951 (van den Berg et al, 2022)	Preventing bleeding will reduce the incidence of sepsis. Chitin has antimicrobial properties (Riaz Rajoka et al, 2020)	Yes
Severe complications	Hospitalisation	UK: average hospital bed cost, £423 per night (https://www.finder.com/uk/healthcare-costs-by-country)	Preventing/reducing the complications identified will prevent/reduce the likelihood of hospitalisation (Lyhne et al, 2022)	Yes

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6. CONCLUSION

CELOX™ PPH offers a safe, rapid, and effective solution for controlling postpartum haemorrhage (PPH). It has been shown to achieve 100% haemostasis for grade 1 and 2 bleeds (up to 2500mls) in all deliveries, significantly reducing the need for hysterectomies compared to current standard of care. CELOX™ PPH is easy to use, requiring minimal training. Moreover, its unique mode of action acts independently of traditional clotting pathways, reducing the necessity for further interventions. With 12 years of clinical efficacy in comparison to standard of care, CELOX™ PPH is proven to be both safe and clinically effective. Its versatility makes it suitable for use in any setting in both developed and developing nations. This document provides a comprehensive summary of the current pre-clinical and clinical evidence supporting CELOX™ PPH as an effective haemostatic agent for management of uterine PPH.

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8. INDEX

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9. APPENDICES

9.1. APPENDIX 1 – tables

Table 1. Complications leading to 75% of all maternal deaths (WHO, 2019)

Severe bleeding (mostly bleeding after childbirth)
Infections (usually after childbirth)
High blood pressure during pregnancy (pre-eclampsia and eclampsia)
Complications from delivery
Unsafe abortion

Table 2. Definition of PPH (NATA Consensus Statement, Muñoz et al (2019))

PPH (level of blood loss)	Definition
Primary	Blood loss of >500 ml within 24 h, whatever the mode of delivery
Severe	Ongoing blood loss of >1,000 ml within 24 h or blood loss accompanied by signs/symptoms of hypovolaemia, whatever the mode of delivery
Massive (life-threatening)	Ongoing blood loss of >2,500 ml or hypovolemic shock, whatever the mode of delivery

Table 3. Overview of regional estimates of the prevalence of PPH and severe PPH (%) (Calvert et al, 2020)

	>500ml	>1000ml	>1500ml	>2000ml
Overall	10.8	2.8		
European Union	12.7	3.8		
Wales[1]		8.6	3.3	1.3
US	13.1	4.3		
Africa	25.7	5.1		
Asia	8.5	1.9		

[1]Data from Bell et al (2020)

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Table 4. Antenatal and intrapartum risk factors for PPH (modified from American College of Obstetricians and Gynecologists, 2006)

Aetiology/primary problem	Risk factors
Uterine atony	Includes prolonged use of oxytocin, high maternal parity, general anaesthesia, conditions resulting in uterine distension (e.g. twins/multiple gestation), macrosomia, uterine fibroids
Uterine inversion	Includes excessive umbilical cord traction, short umbilical cord, fundal implantation of the placenta
Genital tract trauma	Includes operative vaginal delivery (e.g. forceps delivery, vacuum extraction), precipitous delivery resulting in cervical, vaginal, and/or perineal lacerations
Retained placental tissue	Includes succenturiate placental lobe(s), placenta Accreta, Increta, or Percreta
Coagulation disorders	Includes abnormal bruising, preeclampsia, inherited clotting factor deficiency, therapeutic anticoagulation

Table 5. FIGO recommendations for the PREVENTION of PPH (2022)

1	The use of uterotonics for prevention of PPH during the third stage of labor is recommended for all births.	WHO, 2012a; WHO, 2018
2	Oxytocin (10 IU, IV/IM) is the recommended uterotonic drug for the prevention of PPH for vaginal delivery and caesarean section.	WHO, 2012a; WHO, 2018
3	In settings where oxytocin is unavailable or its quality cannot be guaranteed, the use of other injectable uterotonics (if appropriate ergometrine/methylergometrine 200 Qg IM/IV; hypertensive disorders can be safely excluded prior to its use) or oral misoprostol (400–600 Qg orally) or carbetocin 100 Qg IM/IV is recommended for the prevention of PPH.	WHO, 2012a; WHO, 2018
4	The combinations of ergometrine plus oxytocin or misoprostol plus oxytocin may be more effective uterotonic drug strategies for the prevention of PPH ≥500 ml compared with the current standard, oxytocin.	Gallos et al, 2019.
5	In settings where skilled birth attendants are not present to administer injectable uterotonics and oxytocin is unavailable, the administration of misoprostol (400–600 Qg orally) by community healthcare workers and lay health workers is recommended for the prevention of PPH.	WHO, 2012a; WHO, 2018
6	In settings where skilled birth attendants are unavailable, controlled cord traction (CCT) is not recommended.	WHO, 2012a
7	Sustained uterine massage is not recommended as an intervention to prevent PPH in women who have received prophylactic oxytocin.	Hofmeyr et al, 2013
8	Postpartum abdominal uterine tonus assessment for early identification of uterine atony is recommended for all women.	WHO, 2012a
9	Oxytocin (IV or IM) and CCT is the recommended method for removal of the placenta for the prevention of PPH in caesarean delivery.	WHO, 2012a

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Table 6. Treatments used for PPH

Medication to stimulate uterine contractions
Empty bladder to optimise uterine contractions
Uterine massage to stimulate uterine contractions
Removal of placental remnants from the uterus to allow the uterus to contract effectively
Repairing of vaginal, cervical, uterine tears or lacerations
Uterine haemostatic gauze packing / tamponade to apply pressure, control bleeding, and promote haemostasis
Uterine balloon tamponade (UBT) to apply pressure on the uterine walls
Blood transfusion to replenish blood volume
Compression sutures to apply pressure to the uterus to control bleeding
Uterine artery embolization (UAE) to block blood flow to the uterus and reduce bleeding

Table 7. FIGO recommendations for the TREATMENT of PPH (2022) part 1

1	Intravenous oxytocin alone is the recommended first-line uterotonic drug for the treatment of PPH.	Lalonde, 2012; WHO, 2012a
2	If intravenous oxytocin is unavailable, or if the bleeding does not respond to oxytocin, the use of intramuscular ergometrine, oxytocin–ergometrine fixed dose, or a prostaglandin drug (including sublingual misoprostol, 800 Qg) is recommended.	Lalonde, 2012; WHO, 2012a; International Federation of Gynecology and Obstetrics, 2022; Morris et al, 2017
3	There is no evidence about the safety and efficacy of an additional 800-Qg dose of misoprostol for treatment of PPH when given to women who have already received 600 Qg of prophylactic misoprostol orally.	
4	The use of isotonic crystalloids is recommended in preference to the use of colloids for the initial intravenous fluid resuscitation of women with PPH.	WHO, 2012a; Perel et al, 2013
5	Early use of intravenous tranexamic acid as soon as PPH is diagnosed but within 3 hours of birth in addition to standard care is recommended for women with clinically diagnosed PPH following vaginal birth or caesarean delivery.	WOMAN Trial Collaborators, 2017; Shakur et al, 2018
6	Administration of 1 g (100 mg/ml) tranexamic acid intravenously at 1 ml/min (i.e. administered over 10 min), with a second dose of 1 g intravenously if bleeding continues after 30 min, or if bleeding restarts within 24 h of completing the first dose. The scaling up of tranexamic acid for PPH treatment could have a positive impact on health equity and improve outcomes among disadvantaged women, especially those in LMICs thus reducing maternal mortality due to bleeding.	
7	Uterine massage is recommended for the treatment of PPH.	Lalonde, 2012; WHO, 2012a

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Table 7. FIGO recommendations for the TREATMENT of PPH (2022) part 2

8	The use of bimanual uterine compression or external aortic compression for the treatment of PPH due to uterine atony after vaginal birth is recommended as a temporising measure until appropriate care is available.	Lalonde, 2012; WHO, 2012a
9	If women do not respond to treatment using uterotonics, or if uterotonics are unavailable, the use of uterine balloon tamponade (UBT) is recommended as an effective nonsurgical technique that can potentially improve survival in women with PPH due to uterine atony after ruling out retained products of conception or uterine rupture as a contributing factor.	Lalonde, 2012; WHO, 2012a; Tindell et al, 2013
10	Use of the nonpneumatic antishock garment is recommended as a temporizing measure until appropriate care is available.	Lalonde, 2012; WHO, 2012a
11	The use of uterine packing (with a standard gauze) is not recommended for the treatment of PPH due to uterine atony after vaginal birth.	Lalonde, 2012; WHO, 2012a
12	Uterine Artery Embolization (UAE) can be another conservative management measure for PPH if technical conditions and skilled human resources are available for its use.	Mahankali, 2017
13	If bleeding does not stop despite treatment using uterotonics and other available conservative interventions (e.g. uterine massage, balloon tamponade), the use of surgical interventions is recommended. Surgical interventions include the use of compression suture techniques, uterine and hypogastric artery ligation, and hysterectomy.	Lalonde, 2012; WHO, 2012a
14	The priority is to stop the bleeding before the patient develops coagulation problems and organ damage from under-perfusion. Conservative approaches should be tried first, rapidly moving to more invasive procedures if these do not work.	

Table 8. Summary of In vitro studies supporting the effectiveness of chitin-dressings as haemostats part 1

Objectives	Outcomes	Reference
Evaluating the effectiveness of chitin initiating blood coagulation	Chitin dressings reduced clotting time compared with controls	Johnson et al, 2008
Evaluation of the haemostatic effect of the chitosan-derived dressing on coagulation of anticoagulated blood	Chitosan-derived material led to coagulation times similar to those seen in the uncoagulated blood	Johnson et al, 2008
A comparison study of 10 haemostatic dressings in a porcine femoral transection model	The chitosan dressing was found to be one of a group of products with the highest animal survival ($p<0.01$)	Arnaud et al, 2009a
A comparison study of ten haemostatic dressings in a porcine femoral puncture model	Chitosan dressing significantly outperformed ($p<0.01$) and were superior post-treatment blood loss ($p<0.001$)	Arnaud et al, 2009b

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Table 8. Summary of In vitro studies supporting the effectiveness of chitin-dressings as haemostats part 2

Objectives	Outcomes	Reference
Assess blood pressure at which rebleeding occurs after clot formation in porcine femoral injury model after haemostat application	Chitosan dressing stopped bleeding and maintained control as blood pressure increased to >160 mmHg systolic, and was superior to standard dressing (p=0.008)	Burgert et al, 2010
Evaluation of the effect of a chitosan dressing on blood loss in a porcine femoral artery transection model	Significant reduction in blood loss (p<0.01) compared with a standard pressure dressing	Gegel et al, 2010
Assessment of a chitosan gauze in an uncontrolled Haemorrhage model in pigs where no compression was applied	Chitosan gauze was also found to achieve haemostasis in a significant number of cases (6/8)	Watters et al, 2011
In a porcine model of peripheral vascular injury, haemostatic dressings were assessed for their ability to reduce the tourniquet times	The chitosan dressing was successful in maintaining haemostasis in 60% (6/10) of subjects.	MacIntyre et al, 2011
Pre-clinical porcine model of groin arterial Haemorrhage to assess reduction in survival	The chitosan gauze achieved 90% survival compared with 50-70% in other dressings	Rall et al, 2013
In a goat arterial injuries model, several chitosan-derived dressings were tested for haemostasis	All chitosan-containing hemorrhagic dressings performed equally well in promoting haemostasis at 2 and 4 minutes	Satterly et al, 2013
Evaluation of the efficacy of haemostatic dressings in a femoral artery porcine model	All products were similar in initial haemostasis, levels of blood loss and rebleeding and required only minimal training	Conley et al, 2015
Coagulopathic Bleeding Models		
Effectiveness of chitosan haemostats in a model of hepatic injury in presence of clotting dysfunction	Both the chitosan gauze and granules achieved haemostasis in 100% cases	Millner et al, 2010
A chitin-coated gauze (vs normal gauze) was evaluated in a warfarinized blood in a femoral artery bleeding rat model	The chitosan-derived gauze achieved haemostasis in 100% (8/8) cases. The control treatment was successful in only 25% (2/8)	Köksal et al, 2011
Effectiveness of a chitin dressings as a haemostat in a heparinised porcine femoral artery model	Haemostasis was successfully achieved in all subjects (12/12) compared with no haemostasis on the control group	Millner et al, 2011
Laboratory Evaluations		
Rotational thromboelastometry (ROTEM) used to assess speed of clot formation and clot firmness	Chitosan dressing-initiated clots were firmer and better stabilized compared with normal blood clots	Lechner et al, 2016
Experimental evaluation of blood coagulation in patients presenting to ER receiving anticoagulant	Chitosan dressing improved the coagulation of anticoagulated blood	Bar et al, 2017

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Table 9. Proportion of time to haemostasis (UBPP group) (Henrich et al, 2022)

Time to haemostasis	Outcomes	Reference
N (%) 95% confidence interval	83 (91.2%) [85.4 – 97.0]	8 (8.8%) –

Table 10. Success rates for CELOX™ GAUZE results compared with Bakri literature

Success rate for CELOX™ GAUZE			Success rate for Bakri (see Note)		
Overall	Vaginal	C-section	Overall	Vaginal	C-section
91.2% 83/91	94.3% 50/53	86.8% 33/38	85.4% 4652/5446	87.1% 1928/2213	80.9% 1564/1933
Note: References: Ruiz Labarta et al (2021); Laas et al (2012); Revert et al (2016); Suarez et al (2020); Darwish et al (2018); Guo et al (2018); Kaya et al (2014); Beckmann and Chaplin (2014); Kong and To (2013); Khalil et al (2011); Vintejoux et al (2015)					

Table 11. Success rates for CELOX™ PPH results compared with Bakri Balloon literature based on PPH grade

Time to haemostasis				Reference			
Grade	Overall	Vaginal	C-section	Grade	Overall	Vaginal	C-section
Grade 1	100% 21/21	100% 5/5	100% 16/16	Grade 1,2[d,f]	85.6% 143/167	N/A	85.6% 143/167
Grade 2	100% 51/51	100% 12/12	100% 39/39	Grade 2[b,c,i]	85.7% 4275/4991	87.1% 1799/2065	80.9% 1315/1626
Grade 3	57.9% 11/19	66.7% 6/9	50.0% 5/10	Grade 3[a]	31.0% 4/13	N/A	N/A
Grade 1-3	91.2% 83/91	94.3% 50/53	86.8% 33/38	Grade 1 - 3[a,e,g,h]	79.7% 169/212	89.2% 75/84	74.2% 95/128
a: Ruiz Labarta et al (2021); b: Revert et al (2016); c: Suarez et al (2020); d: Guo et al (2018); e: Kaya et al (2014); f: Beckmann and Chaplin (2014); g: Kong and To (2013); h: Khalil et al (2011); i: Vintejoux et al (2015)							

Table 12. Ease of CELOX™ PPH application/removal (FAS group)

Time to haemostasis	Yes (%)	No (%)
N (%) 95% confidence interval	– –	100 (100%) [100 – 100]

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Table 13. Descriptive comparison of advantages and disadvantages of CELOX™ PPH and Bakri balloon tamponade (Dueckelmann et al, 2019)

	CELOX	Bakri
Application	Easy	More difficult
Dislocation	None	Possible
Local haemostatic effect	Yes	No
Pain	Less	More painful
Possible use intravaginally	Yes	No
Possible combination with other measures (sutures)	Yes	Yes
Inflammation	CRP lower	CRP elevated
Presence of drainage	Opening of the cervix may be sealed/blocked, possible collection of blood above the gauze	Yes
Compression of uterine vessels	Low	High
Approval	Off-label use in obstetrics	FDA approved
Costs	Cost-effective	More expensive
Uterine rupture	No published cases	Rare

Table 14. Cost estimates of maternal morbidity conditions in the United States for the 2019 birth cohort (in millions $)

Maternal morbidity	Total	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Amniotic fluid embolism	4.4	4.4	0.0	0.0	0.0	0.0	0.0
Cardiac arrest	10.9	10.9	0.0	0.0	0.0	0.0	0.0
Gestational diabetes mellitus	4843.9	4049.2	158.9	166.1	173.6	181.5	189.7
Haemorrhage	1828.9	1828.9	0.0	0.0	0.0	0.0	0.0
Hypertensive disorders	7540.8	6231.4	261.8	273.7	286.1	299.1	312.6
Maternal mental health	18059.0	9782.6	1655.0	1730.0	1808.4	1890.3	1975.9
Renal disease	3.0	3.0	0.0	0.0	0.0	0.0	0.0
Sepsis	3.3	3.3	0.0	0.0	0.0	0.0	0.0
Venous thromboembolism	6.4	6.4	0.0	0.0	0.0	0.0	0.0
Total	**32300.6**	**21920.1**	**2075.7**	**2169.8**	**2268.1**	**2370.9**	**2478.2**

This table shows the total estimated costs of nine maternal morbidity conditions from conception to five years postpartum, estimated for the US 2019 birth cohort. Maternal morbidity conditions with acute outcomes have one-time costs, while conditions with chronic outcomes have ongoing costs, modelled through five years postpartum.

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Table 15. Costs associated with PPH complications and the favorable influence of CELOX™ PPH on potential cost savings

Complication	Treatment	Associated cost	Positive impact	Cost reduction
Anaemia	Transfusion	Europe: transfusion of two units of blood – €877.69 (Abraham and Sun, 2012) USA: transfusion of one unit of blood – range $900-$3,500 (https://www.thepricer.org/blood-transfusion-cost/)	Reduce blood loss and need for transfusion (Hatamabadi et al, 2015, Carles et al, 2017, Henrich et al, 2023)	Yes
Hypovolemic shock	Transfusion		Reduce blood loss and need for transfusion	Yes
Coagulation disorders	Transfusion, blood product		Stimulation of haemostasis (Pozza et al, 2011, Hatamabadi et al, 2015, Millner et al, 2009)	Yes
Hysterectomy	Surgery	UK: peripartum hysterectomy, mean adjusted additional cost: £5,380 (Achana et al, 2017) US: laparoscopic and vaginal costs $11,637 and $12,229, respectively (Kohn et al, 2022)	A hysterectomy with persistent bleeding was treated through pelvic packing with CELOX™ PPH that stopped bleeding (Carles et al, 2017)	Yes
Infection/ sepsis	Medical treatments, extended hospital stays, ICU care, surgical procedures, medications, diagnostic tests, and follow-up care	Mean total hospital costs per patient (globally), range €1,101 – €91,951 (van den Berg et al, 2022)	Preventing bleeding will reduce the incidence of sepsis. Chitin has antimicrobial properties (Riaz Rajoka et al, 2020)	Yes
Severe complications	Hospitalisation	UK: average hospital bed cost, £423 per night (https://www.finder.com/uk/healthcare-costs-by-country)	Preventing/reducing the complications identified will prevent/reduce the likelihood of hospitalisation (Lyhne et al, 2022)	Yes

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9.2. APPENDIX 2 – Clinical Study Summaries

Postpartum Haemorrhage: CELOX™ PPH retrospective data analysis report (Charité data).

Henrich, W, Dückelmann A, Giroud D, Sarr Y. Version 1.1 – 19 May 2022.
Retrospective analysis study (n=102) (Section 4.3.1)

OBJECTIVE(S)

To evaluate the performance and effectiveness of CELOX™ PPH used in controlling uterine bleeding for primary postpartum Haemorrhage (PPH). Secondary objectives were to evaluate the safety and performance of the CELOX™ PPH in terms of ease of application and ability to remain in situ for up to 24 hours.

INTRODUCTION

PPH is a major cause of maternal death. The main causes of PPH are uterine atony, retained placenta, placental abnormalities, genital tract laceration, and coagulopathies. Based on the latest Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis consensus document, a definition of primary PPH includes blood loss >500ml within 24hrs (grade 1), severe PHH >1000ml within 24hrs (grade 2), and life-threatening PPH >2500ml (grade 3). When PPH does not react to medical treatment, the application of intrauterine balloon as a haemostatic tamponade method is recommended. CELOX™ PPH has been used successfully for many years by the military for managing blood loss. This study is a retrospective analysis on the data from CELOX™ PPH as a treatment for PPH in patients treated at Charité Berlin.

METHODS

Patients presenting with PPH (uterine, vaginal, or cervical) for whom conventional treatment did not work were treated with CELOX™ PPH. Analysis for safety included patients receiving CELOX™ PPH for any intrauterine, vaginal, or cervical bleeding regardless of bleeding cause and regardless of whether used alone or in combination with balloon tamponade. Data was collected from documents for patients treated between October 2016 and June 2018. Successful haemostasis was assessed as halting of bleeding in less than 5 minutes. Safety endpoints was assessed as the proportion of adverse events (including level of additional interventions needed, rate of symptoms of infection, allergic reaction). Two populations were identified in this analysis: a full set population (FAS) (n=102) who were all patients started treatment with CELOX™ PPH regardless of the cause of bleeding, and the uterine bleeding performance population (UBPP) (n=91) who has clear indication of uterine bleeding.

RESULTS

CELOX™ PPH was successful in halting blood loss in 89.2% (91/102) FAS patients, and 91.2% (83/91) UBPP patients. In the UBPP group, 58.2% (53/91) had a vaginal delivery and 94.3% (50/53) reached successful haemostasis with CELOX™ PPH, and 41.8% UBPP patients with uterine PPH required a caesarean section, of which 86.8% (33/38) reached successful haemostasis with CELOX™ PPH. Of the 91 UBPP patients, 23.1% (21/91) had grade 1, 56.0% (51/91) grade 2, and 20.9% (19/91) had grade 3 bleeds. CELOX™ PPH reached 100% successful haemostasis in all patients with grades 1 and 2. For grade 3, the overall success rate was 57.9% (11/19). The infection rate for all patients included in this study was 6.9% (7/102), but no infections were attributable solely and directly to CELOX™ PPH. There was a significant reduction of 77.8% (OR 4.55, P=0.037) in hysterectomies after commencement with compared with before the use of CELOX™ PPH. The average duration of use was 22.2 3 8.1 hrs in the FAS group and 23.0 3 7.14 hrs in the UBPP group.

CONCLUSIONS

This retrospective analysis demonstrates that CELOX™ PPH, as a treatment of PPH has significant positive results both in reaching haemostasis as well as considering its safety profile.

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Uterine packing with CELOX™ PPH compared to balloon tamponade for managing postpartum Haemorrhage.

Dueckelmann AM, Hinkson L, Nonnenmacher A, Siedentopf JP, Schoenborn I, Weizsaecker K, Kaufner L, Henrich W, Braun T. Eur J Obstet Gynecol Reprod Biol. 2019; 240:151-155.

Retrospective cohort study (n=78) (Section 4.3.2)

OBJECTIVE(S)

Assessment of the effectiveness and safety of CELOX™ PPH versus a balloon tamponade for managing severe PPH.

INTRODUCTION

Obstetric Haemorrhage is the world's leading cause of maternal death. Postpartum Haemorrhage (PPH), often caused by uterine atony, is the most common type. Management of this most common type of PPH includes selective devascularisation, application of uterine compression sutures, and intrauterine packing. CELOX™ PPH has been used for the treatment of PPH as an effective tamponade in combination with potential local haemostasis-stimulating properties. The purpose of this retrospective study was to compare the outcomes of CELOX™ PPH with the use of Bakri balloon tamponade.

METHODS

Seventy-eight patients with uterine PPH were included in this study, and 47 (60.3%) received CELOX™ PPH tamponade and 31 (39.7%) received a balloon tamponade. Women with PPH were treated according to management guidelines. When bleeding persisted, additional uterine packing with either CELOX™ PPH or a balloon tamponade. In women treated with CELOX™ PPH, in cases of spontaneous deliveries, the gauze was inserted transvaginally. In cases of caesarean deliveries, the uterine cavity was packed with gauze either through the hysterotomy or transvaginally. In women treated with a balloon tamponade, the device was applied according to manufacturer instructions: the deflated Bakri balloon was inserted into the uterine cavity transvaginally, and the balloon was inflated with water. The primary outcome was halting of uterine bleeding without additional surgical interventions. Secondary outcomes included the amount of blood loss, the amount of blood transfusions and maternal complications.

RESULTS

The two groups were not statistically different with respect to the outcomes monitored: postpartum vital signs, haemoglobin levels, blood loss, admission to intensive care, or inflammation parameters showed no significant difference. Both treatment modalities successfully controlled primary atonic PPH in most cases. Three patients in the balloon tamponade group required a hysterectomy. No hysterectomy was required in the CELOX™ PPH group.

During an observation period of 18 months before (5414 deliveries) and 18 months (5430 deliveries) after introduction of CELOX™ PPH at one clinic location four and two, respectively, PPH-related hysterectomies had to be performed. Thus, the rate of peripartum hysterectomies was reduced by 50%.

CONCLUSIONS

CELOX™ PPH is an excellent option for treating PPH, and it appeared to be at least equivalent to the balloon tamponade. The clinicians found the CELOX™ PPH to be particularly suited for atony or placenta bed bleeding after spontaneous delivery or during caesarean sections, in cases of lower uterine segment atony, placenta previa bed bleeding, and/or coagulopathy.

No major adverse events or specific treatment-associated morbidity were associated with CELOX™ PPH.

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Comparison of CELOX™ PPH and Bakri balloon in management of primary atonic postpartum Haemorrhage.

von Beckerath AK, Maul H, Elmohandes AM, Shaaban M, Habib DM, Nasr A, Abdel-Kawi AF. Am J Obstet Gynecol. 2016; 214(1 Suppl 1):S335. [poster presentation]

Randomised, prospective study (n=61) (Section 4.3.3)

OBJECTIVE(S)

Assessment of the effectiveness of CELOX™ PPH versus a balloon tamponade for managing atonic postpartum Haemorrhage (PPH).

INTRODUCTION

PPH is the world's leading cause of maternal death. PPH, often caused by uterine atony, is the most common type. Mechanical compression techniques such as balloon tamponade have been used in the management of primary atonic PPH in cases where medical uterotonic agents failed. CELOX™ PPH has been used for the treatment of PPH as an effective tamponade in combination with potential local haemostasis-stimulating properties. This study was designed to show the effectiveness of intrauterine insertion of CELOX™ PPH in comparison to the standard application of a balloon tamponade (Bakri).

METHODS

This was an unblinded randomised parallel prospective study. Sixty-one patients with uterine PPH were included in this study, and 31 (50.8%) received CELOX™ PPH and 30 (49.2%) received a balloon tamponade. The primary endpoint was the need for any further surgical interventions (e.g., peripartum hysterectomy) as a failure of the mechanical method. Secondary endpoints included post-insertion fever and admission to the intensive care unit.

RESULTS

A failure rate which led to peripartum hysterectomy was found to be 9.7% (3/31) in the CELOX™ PPH group compared to 40.0% (12/30) in the balloon tamponade group. low-grade fever (38.0-38.5°C) was recorded in 19.4% (6/31) of the CELOX™ PPH group compared with none (0.0%) in the balloon tamponade group. Admission to the intensive care unit was 41.9% (13/31) in the CELOX™ PPH group (with an average stay of 5 days) compared to 33.3% (10/30) in the balloon tamponade group (with an average stay of 7 days).

CONCLUSIONS

From the findings of this preliminary study, the clinicians concluded that CELOX™ PPH appears to be a potentially effective method in the management of atonic PPH. Furthermore, the clinicians note that CELOX™ PPH is inexpensive, easy to use, and has well managed side effects compared to the use of a standard intrauterine balloon tamponade.

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Does the use of CELOX™ PPH for postpartum Haemorrhage reduce the need for surgical therapy including hysterectomy? A databased historical cohort study.

Biele C, Radtke L, Kaufner L, Hinkson L, Braun T, Henrich W, Dückelmann AM. J Perinat Med. 2022; 50(8):1078-1086.

Retrospective cohort study (n=666) (Section 4.3.4)

OBJECTIVE(S)

To compare the therapy success of CELOX™ PPH tamponade with a balloon tamponade and medical therapy only in the treatment of postpartum Haemorrhage (PPH).

INTRODUCTION

PPH is the primary cause of maternal morbidity and mortality worldwide. Therapy options vary with the degree of severity from medical therapy over uterine packing techniques to surgical measures: compressing sutures, selective devascularization and postpartum hysterectomy (HE), the last therapeutic resort associated with high morbidity and the loss of fertility. Medical therapy is the first line therapy in PPH and consists of the use of uterotonic and haemostatic drugs. In cases of persistent bleeding uterine packing is an option to control Haemorrhage and prevent surgical therapy. A well-established uterine tamponade is the balloon tamponade. This databased retrospective case–control study compares the therapy success of a CELOX™ PPH tamponade with that of the balloon tamponade and medical therapy only.

METHODS

A total of 666 women were included in this study. women were divided into three groups: medical therapy only (n=530, 79.6%), balloon tamponade (Bakri) (n=51, 7.7%) and CELOX™ PPH tamponade (n=85, 12.8%). The groups were compared in terms of therapy success, side-effects and reasons for PPH. Primary outcome was the need for surgical/radiological measures including hysterectomy. Secondary outcomes were differences in haemoglobin levels, duration of inpatient stay, admission to intensive care unit, number of administered blood products and inflammation parameters.

RESULTS

There were no significant differences in the need for surgical therapy between the three groups. However, there were a significantly lower number of hysterectomies in the CELOX™ PPH group compared with the balloon tamponade group. There were no relevant differences in secondary outcomes and no adverse events related to the CELOX™ PPH group. In the 31 months after the implementation of CELOX™ PPH tamponade two hysterectomies out of 9,167 births due to PPH were necessary, and in 31 months before implementation of CELOX™ PPH nine hysterectomies out of 9,058 births were performed, a reduction of 77.8%.

CONCLUSIONS

The clinicians conclude that CELOX™ PPH is a promising treatment for PPH. The study indicated a significant reduction in the rate of hysterectomy after the implementation of CELOX™ PPH, and the clinicians suggest that these positive findings may be the result of the combination of the CELOX™ PPH tamponade's compressing property and the coagulating properties of chitosan. No side effects were noted. The clinicians suggest that CELOX™ PPH may be a superior treatment option compared to balloon tamponade in terms of clinical effectiveness and application. It is easy to use and is inexpensive compared with other treatment options. In addition, they suggest that the early use of CELOX™ PPH in patients with a high risk of bleeding is justified.

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Use of CELOX™ PPH in 98 cases of severe postpartum Haemorrhage - a multicenter registry analysis.

von Beckerath AK, Maul H, Gebauer G, Abdel-Kawi AF, Rolf N, Saade G, Bader W, Kusnierczak D, Berger R, Kienast C, Kienemund J, Schmid B. Am J Obstet Gynecol. 2016; 214(1 Suppl 1):S269. [poster presentation]

Multicentre registry analysis study (n=98) (Section 4.3.5)

OBJECTIVE(S)

To assess on potential side effects of CELOX™ PPH in cases on postpartum Haemorrhage (PPH).

INTRODUCTION

PPH is the world's leading cause of maternal death. PPH, often caused by uterine atony, is the most common type. Mechanical compression techniques such as balloon tamponade have been used in the management of primary atonic PPH in cases where medical uterotonic agents failed. Chitosan is a haemostatic agent and CELOX™ PPH was originally developed for military traumatology. CELOX™ PPH has been used for the treatment of PPH. The objective of this multicenter registry analysis is to report on potential side effects of CELOX™ PPH and to verify if the use of CELOX™ PPH reduces the rate of postpartum hysterectomies.

METHODS

Women suffering from PPH were treated according to guideline management and by additional uterine packing with CELOX™ PPH, if bleeding persisted. In addition, clinical data were compared with a 26-month period before introduction of CELOX™ PPH with the same basic management of PPH. Reduction of postpartum hysterectomies was evaluated.

RESULTS

CELOX™ PPH was used in 98 cases of PPH. In all cases C-reactive protein levels (an indicator of inflammation) were elevated, as was leukocyte numbers. Ten patients (10.2%) developed fever, however none of the patients exhibited sepsis. In six (6.1%) cases of severe PPH a hysterectomy was necessary. After the introduction of CELOX™ PPH the rate of postpartum hysterectomy was significantly reduced (0.05% vs. 0.18%, OR 0.28; p¼0.0183). Two patients had an uncomplicated pregnancy following treatment with CELOX™ PPH. Maternal mortality was zero (0%) after the introduction of CELOX™ PPH.

CONCLUSIONS

This preliminary study concluded that CELOX™ PPH can be used effectively in treating severe cases of PPH. To date, no major adverse events have been observed or reported. In addition, the use of CELOX™ PPH significantly reduces the number of postpartum hysterectomies. The clinicians note that the CELOX™ PPH is easy to apply and is cost-efficient.

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9.3. APPENDIX 3 – Instructions for use

INSTRUCTIONS FOR USE

Uterine Haemostatic Tamponade

INTENDED PURPOSE:
CELOX™ PPH is intended to be a physical haemostat for control of emergency bleeding.

INDICATION FOR USE:
CELOX™ PPH is intended to be applied and removed vaginally to provide control and treatment of uterine postpartum haemorrhage when conservative management is warranted.

DESCRIPTION:
CELOX™ PPH is a uterine haemostatic tamponade provided in a z-fold/concertina format. It has CELOX™ haemostatic granules loosely adhered to a fabric (3m x 7.6cm).

PATIENT GROUP:
Females of childbearing age.

USERS:
The product is intended for use by physicians and midwives trained and experienced in obstetrical techniques.

CLINICAL BENEFIT:
Postpartum haemorrhage can be life-threatening. The use of the device will reduce the likelihood of needing hysterectomy (or other interventional methods) by controlling postpartum haemorrhage.

CONTRAINDICATIONS
- Subjects who present with uterine rupture.
- Unresolved uterine inversion.
- Current cervical cancer.
- Current purulent infection of the vagina, cervix, uterus.
- Ongoing Pregnancy.

WARNINGS
- Do not use if the primary pack is damaged or open as the device may not be sterile.
- Keep away from liquids prior to use. The CELOX™ granules will gel in contact with liquid, making application difficult and reduce haemostatic effectiveness.
- As with other haemostatic agents, do not aspirate blood into cell saver equipment or autologous blood salvage circuits. There is a potential risk of embolism if the blood is returned to the patient.
- The haemostatic effect of CELOX™ PPH is not enhanced by the addition of topical thrombin, the activity of which may be destroyed by the pH of CELOX™ PPH.
- CELOX™ PPH must not be used as a vaginal/cervical pack for uterine postpartum haemorrhage as uncontrolled bleeding could continue in the uterus.
- For single use only. Re-use could potentially result in the risk of infection and lack of device performance.
- If the patient develops high fever (>38°C) following haemostasis remove the device.
- Do not leave CELOX™ PPH for longer than 24h in the body due to possible risk of infection.
- Transvaginal application of CELOX™ PPH may not be possible when cervix dilation has not started e.g., in case of elective c-section.
- Do not use suturing techniques (e.g., uterotomy closure, B-Lynch, Pereira) whilst CELOX™ PPH is in the uterus as this may result in CELOX™ PPH being incorporated into the suture causing difficulty for removal and risk of product tearing.

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INSTRUCTIONS FOR USE

Uterine Haemostatic Tamponade

PRECAUTIONS

- If used concurrently with compression suturing e.g., B-Lynch, the sutures should be applied prior to CELOX™ PPH application to avoid excessive compression by the procedure resulting in difficulty to remove the CELOX™ PPH after treatment completion.
- Caution is advised when suturing (e.g., for vaginal or cervical tears) that CELOX™ PPH is not included in the stitch, which upon removal of CELOX™ PPH may tear leaving a fragment attached to the stitch.
- During use avoid excessive manipulation of the patient when transferring to hospital or between departments as this may disturb the device, potentially resulting in rebleed.

STORAGE

There are no special storage conditions required for the device, except to keep the shipper cases and instruction leaflet dry.

INSTRUCTIONS FOR USE

- CELOX™ PPH should be used when postpartum haemorrhage does not respond to initial management such as uterine massage, volume replacement, and standard medical treatment with uterotonic and antifibrinolytic agents.
- Tear open the package at the tear notches. Sterile technique should be observed in delivering the sterile CELOX™ PPH to the field of application.
- After caesarean deliveries ensure the uterotomy is closed prior to applying the device transvaginally.
- Ensure any retained placenta tissue, blood clots or membranes are removed from the uterus prior to uterine packing with CELOX™ PPH.
- Remove any equipment applying external pressure to the uterus (e.g., pressure pads) prior to applying the device.
- Use at least one CELOX™ PPH for each patient and do not cut or tear CELOX™ PPH prior to application as this could increase the risk of material fragments being left in the uterus. Use a maximum of 2 CELOX™ PPH per patient over the course of treatment.
- Allow the CELOX™ PPH to unfold externally to the patient whilst applying the device.
- Place the patient in a lithotomy position, and with the aid of a speculum grasp the cervix with an atraumatic instrument, if necessary, and manually insert the unfolding CELOX™ PPH into the uterine cavity with atraumatic forceps up to the fundus. Avoid excessive force and use ultrasound guidance if available to guide application to ensure the device reaches the site(s) of bleeding and to minimise the risk of damaging the uterine wall. If ultrasound is not available, use external manual palpation to avoid injury to the uterine wall by the insertion device.
- CELOX™ PPH must contact the site(s) of bleeding.
- CELOX™ PPH should be used to cover the uterine wall and if needed use secondary sterile dressings/gauze (non CELOX™) for packing. Leave sufficient length of the end of each CELOX™ PPH protruding through the cervix and vagina to allow subsequent removal.
- If needed, the vagina may be packed with secondary sterile dressings/gauze (non CELOX™) for compression of ascending vessels.
- While CELOX™ PPH is in place, compression is to be applied for a sufficient duration according to clinical judgement to enable haemostasis.
- If postpartum haemorrhage continues, remove CELOX™ PPH and revert to the next stage of the standard of care/protocol for post-partum haemorrhage.
- Following haemostasis, excess CELOX™ PPH can be cut from the ends protruding from the vagina (leaving sufficient length of each CELOX™ PPH to be noticeable and to allow removal).
- Dispose of any excess material and packaging as per local clinical waste management guidelines.

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INSTRUCTIONS FOR USE

Uterine Haemostatic Tamponade

- Use local standards of care to identify the number of CELOX™ PPH that have been applied to the patient e.g., use of wristbands. Identify in the patient file that CELOX™ PPH has been used and indicate when it needs to be removed. Ensure the patient is informed CELOX™ PPH is in place and needs to be removed by a professional within 24hrs.
- Monitor the patient carefully for signs of rebleeding (e.g. clinical signs, monitoring of blood values and using ultrasound scans if available). Treatment with oxytocic/uterotonic drugs may continue during this time.
- Closely monitor for signs disseminated intravascular coagulation (DIC), and in such cases, emergency intervention per hospital protocol should be followed.
- Leave CELOX™ PPH in place for 24 hours if clinically feasible, but no longer.
- CELOX™ PPH should be removable by pulling the end left outside the vagina.
- Upon removal, inspect the end of the fabric for an intact edge to determine integrity and completeness. Adequate revision action steps should be initiated when incomplete removal is observed or suspected. No fabric fragments should be left behind.
- Dispose of the used CELOX™ PPH according to standard hospital procedures for clinical waste.
- It is expected loose residual granules or gelled material from CELOX™ PPH will be expelled in the lochia of the patient and potentially upon menstruation restarting. This could potentially be several weeks after use. This information should be conveyed to the patient.

ADDITIONAL INFORMATION

- Not made with natural rubber latex.
- The device is effective in patients that are coagulopathic.
- CELOX™ PPH and residuals are not intended to be absorbed by the body.
- The safety and effectiveness of CELOX™ PPH with other topical haemostatic agents or sealants/adhesives has not been established.
- Contains chitosan from shellfish, allergy studies showed no adverse reactions to similar chitosan.
- The Summary of Safety and Clinical Performance (SSCP) for the device is available in the European database on medical devices (Eudamed), where it is linked to the Basic UDI-DI. The Eudamed website is https://ec.europa.eu/tools/eudamed and the Basic UDI-DI is 5060206630883817l2L.
- Any serious incident that has occurred in relation to the device should be reported to the manufacturer and the competent authority of the Member State in which the user and/or patient is established.

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FAST ACTING | SAFE AND CLINICALLY EFFECTIVE | VERSATILE AND EASY TO USE

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