

SNAPSHOT OF THE R&D LANDSCAPE OF POSTPARTUM HAEMORRHAGE DEVICES (2000-2023)

MAY 2023



AIM

ACCELERATING
INNOVATION FOR MOTHERS

AIM was established in 2020 to reinvigorate investment and spur research and development of maternal health products for significant pregnancy-specific conditions where biomedical product gaps exist



POSTPARTUM HAEMORRHAGE

Innovation needed to reduce maternal mortality

Postpartum haemorrhage (PPH) is defined as blood loss of 500mL or more after birth. It is the leading cause of maternal mortality worldwide, responsible for over one-fifth of all maternal deaths globally, the greatest burden of which are felt in low- and middle-income countries (LMICs).¹ Despite an international commitment to reduce the global maternal mortality ratio to 70 deaths per 100,000 live births by the year 2030, several countries are expected to fall short.²

While medicines are the cornerstone of PPH prevention and treatment, the current catalogue is suboptimal, particularly for LMIC settings where issues related to quality, cold-chain transport and storage, and skilled administration limit access.³ Low-tech medical devices can serve as an important intervention when medications fail or are unavailable, with some (uterine balloon tamponades) currently recommended by the World Health Organization (WHO) for treatment of PPH for women who do not respond to standard first-line treatment.⁴

Use of devices in the management of PPH is fairly recent, however. Outside of anti-shock garments, the first case report on the use of a device in managing PPH was in 1985, when a Foley Catheter was used as a uterine balloon tamponade device (UBT).⁵ More than fifteen years later in 2001, the first purpose-built PPH device – the Bakri Balloon – was developed.⁶ In the intervening years, the landscape of PPH devices has evolved, but even for those recommended for use, many still lack strong evidence for efficacy.⁴

Despite a clear need for innovation, the PPH biomedical product landscape remains sluggish.³ Improved medicines will be critical to improving PPH outcomes, however innovations in low-tech approaches such as devices will also be essential to shoulder the burden of reducing deaths due to PPH, particularly in resource-limited settings.

The 'Accelerating Innovation for Mothers' (AIM)⁷ project – spearheaded by the Concept Foundation and delivered in partnership with Policy Cures Research and the Burnet Institute – was established in 2020 to reinvigorate investment and spur research and development (R&D) of maternal health products for significant pregnancy-specific conditions where biomedical product gaps exist. A key objective was to develop the first comprehensive pipeline database of maternal health products in development over the past two decades, including all devices in use or investigated for PPH between 2000 and 2023.⁸ This report presents data on the latter, to provide an up-to-date snapshot of the R&D landscape for this critical maternal health intervention.

OVERVIEW OF THE PPH DEVICES PIPELINE

In total, 36 devices were identified as in use or investigated for PPH between 2000 and 2023. One-third were already approved for use (12 devices, 33%) – all necessarily in post-marketing studies – and two-thirds were under investigation (24 devices, 67%). Of the latter, 88% (21) were in human safety & efficacy trials, with just three in discovery and preclinical stages.

Across all 36 devices, 21 (58%) were in active development (had evidence of R&D activity within the last three years), whereas the remaining 15 (42%) were inactive, all due to lack of evidence of activity within the last three years, as opposed to product terminations.

Of the 12 approved devices, recent (under 3 years old) publications or news items were identified for nine devices, including the original Bakri Balloon, the JADA System and the Ellavi Uterine Balloon Tamponade. Amongst the 24 investigational candidate devices, half (12) were under active investigation. These include a number of balloon tamponades already used off label for PPH (e.g., condom catheter, glove tamponade, Foley catheter, and Cook Cervical Ripening Balloon), as well as a range of other new investigational devices including the Mini-Sponge Tamponade Device, Suction Tube Uterine Tamponade (STUT) (with Levin tube), PPH butterfly, Hemostatic Intra-Uterine Suction Cup, and quite low-tech devices such as ice packs and a ball and binder. All active investigational devices are undergoing human safety and efficacy studies, with none in discovery and preclinical stages.

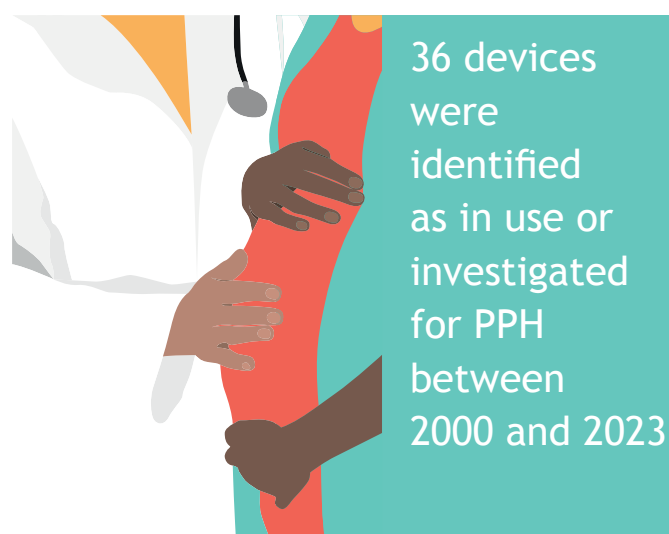
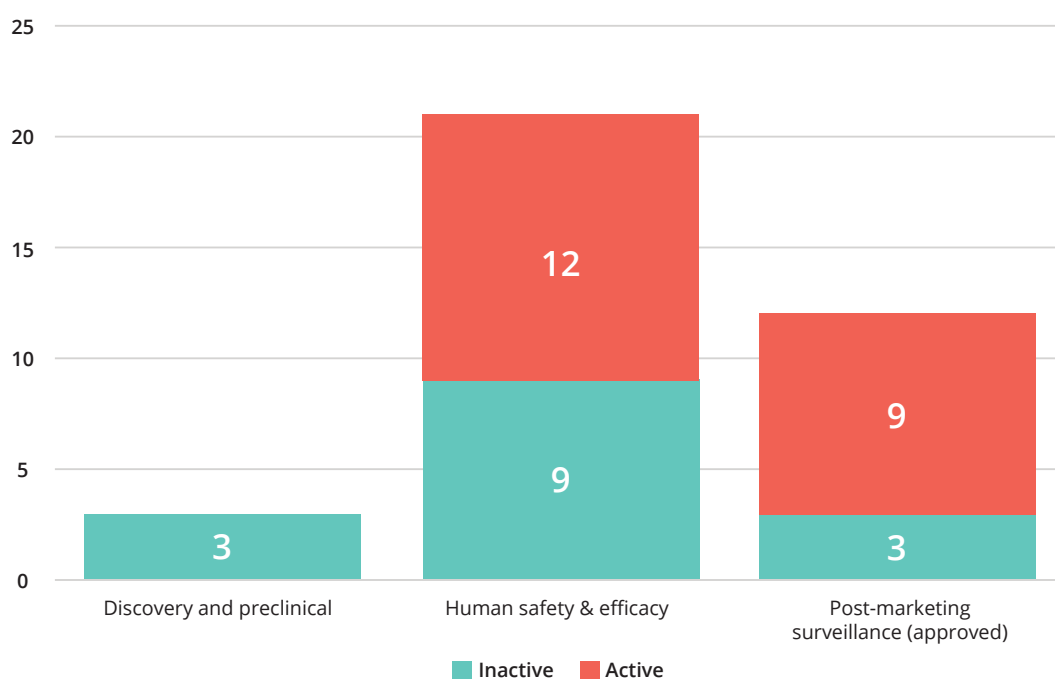


Figure 1: PPH devices by R&D stage and development status (active vs inactive*)

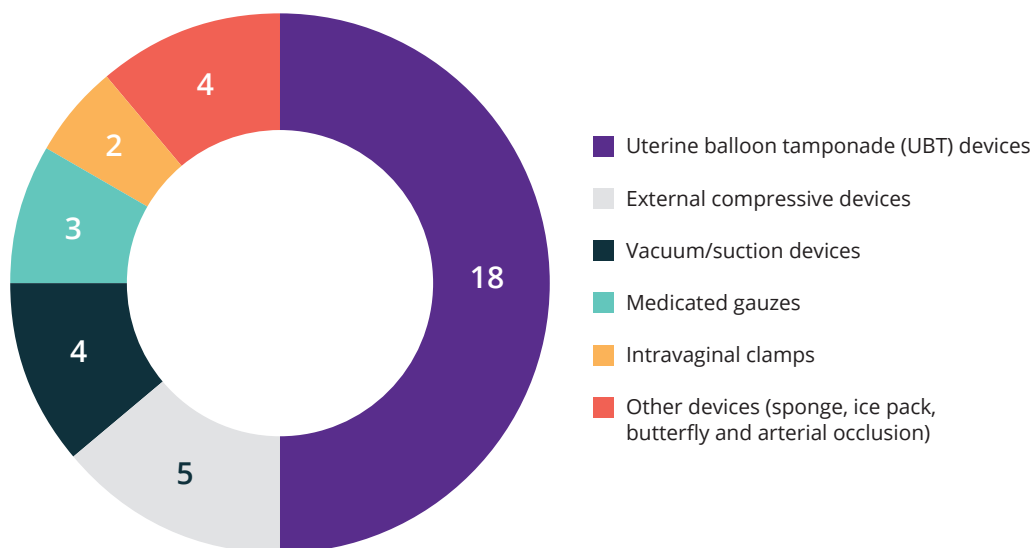


* If no updates were made available on a candidate in the previous three years, or there was clear evidence of their discontinuation since then, they were classified as 'inactive'

Balloons Dominate, But Novel Approaches are Emerging

PPH devices are not uniform, varying widely in placement, concept and mechanism of action. This includes a range of UBT (balloon) devices, external compressive devices, vacuum/suction devices, medicated gauze, intravaginal clamps and other devices such as sponges, vaginally placed ‘butterfly’ devices, arterial occlusion devices and even very basic ice packs for uterine cooling.

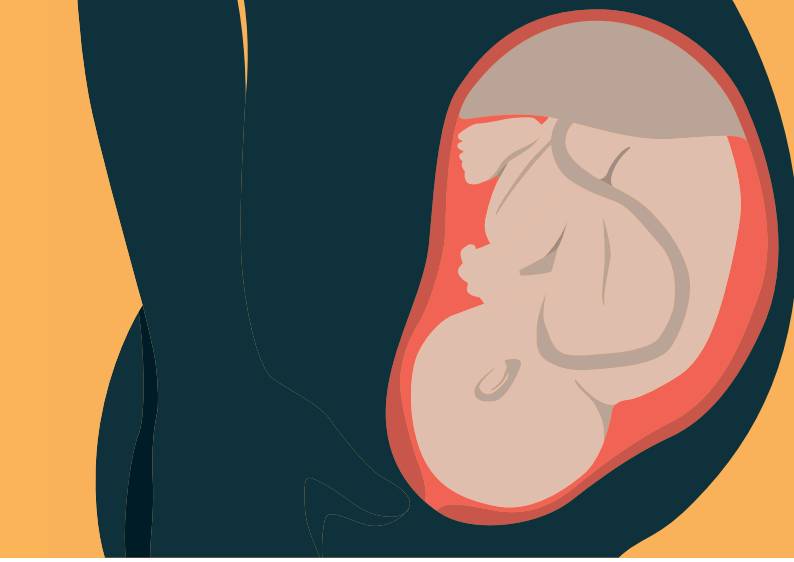
Figure 2: PPH devices by product concept type



More than 80% (29) of PPH devices act by placement inside the uterus or vagina, with the most common of these being UBT devices. In fact, UBTs comprise half of all PPH devices identified (18, 50%). This includes the Bakri Balloon and eight other balloons developed specifically to treat PPH, including the ebb Complete Tamponade System (Belfort-Dildy Balloon), BT-Cath and the Russian Zhukovsky Double Balloon Obstetric Catheter. The remaining nine intrauterine balloons are either repurposed (six devices) – such as the Foley Catheter or Cook Cervical Ripening Balloon – or completely improvised (three), the latter entailing devices including and similar to the Condom Catheter. Overall, half of the balloons were already approved for use, and the remaining half were in clinical development.

Table 1: PPH UBTs (balloons) by archetype: new, repurposed and improvised

New devices		
<ul style="list-style-type: none">● Bakri Balloon● BT-Cath● ebb Complete Tamponade System (Belfort-Dildy Balloon)● Ellavi Uterine Balloon Tamponade● Every Second Matters for Mothers and Babies – Uterine Balloon Tamponade (ESM-UBT)● Kyoto Balloon System● Tampostat● Zhukovsky Double Ballon Obstetric Catheter● Novel UBT by Cambridge Design Partnership		
Repurposed devices		Improvised devices
<ul style="list-style-type: none">● Cook Cervical Ripening Balloon● Linton-Nachlas Tube● Metreurynter● Rusch Balloon● Sengstaken-Blakemore Tube		<ul style="list-style-type: none">● Condom Catheter● El-Menia Balloon● Glove Tamponade

An illustration of a fetus in the womb, shown in profile. The fetus is light pink with a darker pink umbilical cord. The womb is a darker pink, and the surrounding area is a dark blue. The background of the entire page is a solid orange color.

Only two-fifths of all devices identified were designed and developed specifically to treat and control PPH

While UBTs accounted for the largest share of PPH devices, they account for only 38% of all devices in active development, indicating a slight trend towards innovative and novel device concepts. Four vacuum/suction devices, for example – that manage PPH by applying negative intrauterine pressure rather than the positive pressure characteristic of nearly all other (28) PPH devices – were identified, all of which were in active development. This includes the US FDA-approved JADA System, an intrauterine soft silicone ring that uses gentle suction to contract the uterus and constrict blood vessels. The JADA System was acquired – along with originators Alydia Health – by MSD’s women’s health spinoff Organon in 2021.

The remaining three vacuum/suction devices are still in human safety & efficacy trials, and comprise the Hemostatic Intra-Uterine Suction Cup, Suction Cannula and the Suction Tube Uterine Tamponade (STUT) device, the latter utilising a repurposed Levin tube. Interestingly, one other device was found to have demonstrated pressure versatility: while the Bakri balloon is designed to promote haemostasis by positive intrauterine pressure, a novel vacuum-induced tamponade technique was trialled in which the Bakri balloon was connected to a vacuum source to apply negative pressure, with the approach labelled the ‘modified Bakri balloon system’.⁹

Another novel concept in the PPH device R&D landscape is medicated gauze, which are used to pack the uterus or vagina. Three types of medicated gauze were identified as approved or under investigation for PPH: HemCon GuardaCare, QuikClot and Celox gauze. The PPH-specific Celox gauze – the CELOX PPH Uterine Hemostatic Tamponade – recently received CE certification in the EU in November of 2022. Celox, alongside Hemcon GuardaCare utilises chitosan to promote haemostasis, whereas QuikClot utilises kaolin. These three medicated gauzes are all repurposed and were originally designed for topical wound care in the military context. All other PPH devices do not include a medicated element.

Four other devices identified are also positioned in the uterus or vagina. This includes two clamps that are placed intravaginally to occlude the uterine arteries, as well as the Mini-Sponge Tamponade Device, a pouch on a string containing a number of small sponges placed in the uterus or vagina that works by rapidly expanding on contact with blood to exert an outward pressure. It also includes the PPH butterfly, an intravaginal device that consists of a perforated platform and folding handle, for which promising phase II clinical trial results were recently published: the device was used in 57 women, and only one woman had additional blood loss of 1000mLs or more, though three women (7%) also required Bakri Balloon placement.¹⁰

Almost all of the remaining devices (six) are placed externally, and mostly comprise compressive devices, such as pneumatic or non-pneumatic body-wrap anti-shock garments, the External Aortic Compression Device, and abdominal binders (the ProCare Abdominal Binder and an improvised simple ball and binder), as well as externally placed ice packs or towels. One device – arterial occlusion balloons – are balloons placed intra-arterially to occlude blood flow to the uterus.

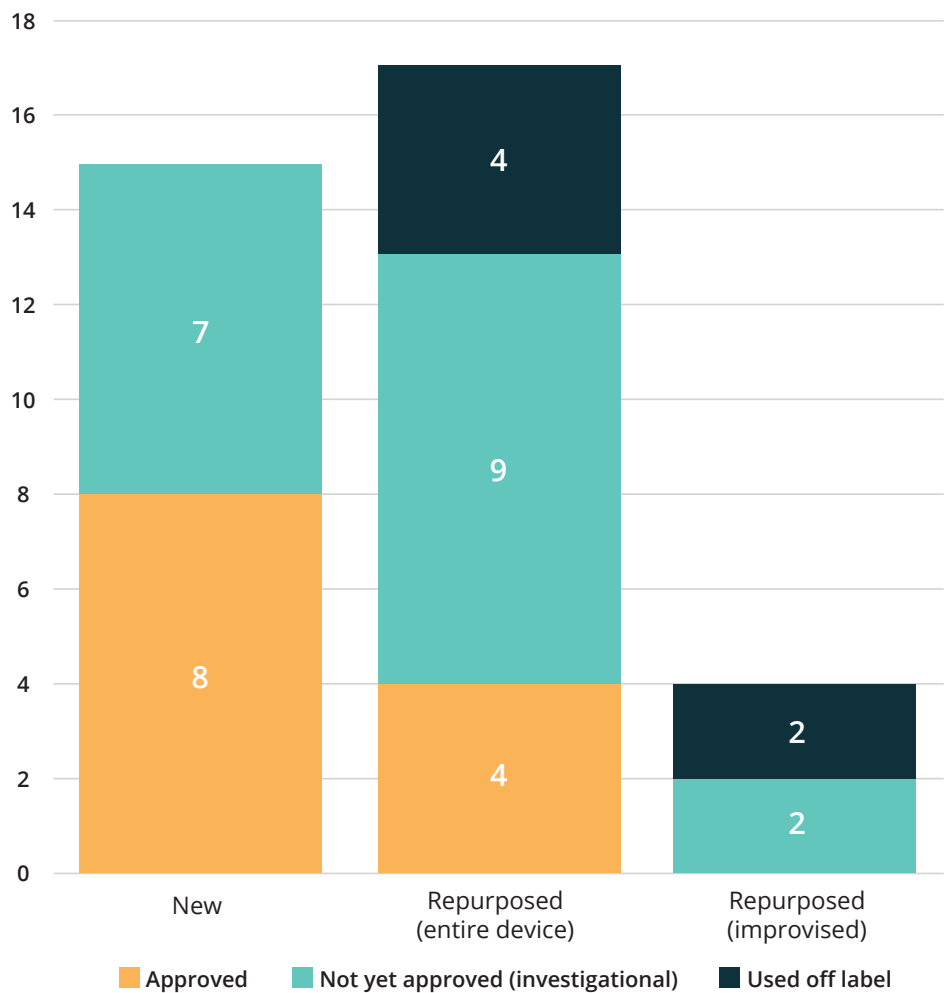
REPURPOSED AND IMPROVISED DEVICES ARE THE NORM

Despite a reasonably-sized body of devices either in use or under investigation for PPH, only two-fifths of all devices identified (15 candidates, 42%) were designed and developed specifically to treat and control PPH. This includes the well-documented first UBT for PPH – the Bakri balloon – as well as PATH and Sinapi Biomedical’s Ellavi Uterine Balloon Tamponade, the Every Second Matters for Mothers and Babies - UBT (ESM-UBT) device from Vayu Global Health Innovations and Massachusetts General Hospital, and the JADA system.

The majority remainder were repurposed devices, in which the entire device was repurposed (17 devices, 47%) – such as pneumatic and non-pneumatic anti-shock garments, gauze-related products, and existing balloon catheters with other indications – or the repurposed device consisted of improvised components (four devices, 11%). The latter mostly comprised devices that utilise condoms, gloves and latex party balloons.

Six of the repurposed devices are used off label for PPH in clinical practice, including the Cook Cervical Ripening Balloon, originally designed for cervical ripening, and the Rusch Balloon, a urinary catheter. Condom Catheters are also used off label in low-resource settings, where purpose-built PPH devices may be too expensive. Encouragingly however, two devices developed specifically to manage PPH were also designed to address LMIC needs. This includes the Ellavi Uterine Balloon Tamponade and the ESM-UBT device, the latter a Condom Catheter kit in which all the device components are packaged together. Both devices are designed to cost less than \$15 USD each and are approved by National Regulatory Authorities in LMICs, alongside the non-pneumatic anti-shock garments. Almost all of the remaining approved devices (eight devices, 67% of approved devices) have received approval by a Stringent Regulatory Authority, except the Zhukovsky Double Balloon Obstetric Catheter, which is approved for use in Russia.

Figure 3: PPH devices by archetype and clinical use status



The PPH R&D landscape will need greater investment to support the development of devices which are fit-for-purpose in low-resource settings and are adequately tested to support their use and widespread roll-out



REFLECTIONS

Since the first reports of the use of a device in managing PPH, the PPH device landscape has grown and diversified. Encouragingly, there now exists a range of devices that differ in concept and mechanism of action, with a slight trend away from traditional balloon tamponades to innovative designs that entail vacuum/suction and sponge devices. Despite this, many reflect the improvisation sometimes needed in low-resource settings to treat women in emergent haemorrhage situations, with few specifically designed for PPH, and an even smaller proportion explicitly purposed as low-cost options for resource-limited settings. Furthermore, the body of evidence to support many of them is limited.⁴ Treating PPH globally will require an arsenal of different tools, and the PPH device R&D landscape still has room to develop.

Unfortunately, investment in PPH device R&D remains extremely low. Since 2018, Policy Cures Research has been tracking global investment in LMIC-appropriate product R&D for a range of sexual and reproductive health issues – including PPH – as part of the G-FINDER project. Between 2018 and 2021 just USD \$1.8m of funding was identified, with figures reported decreasing each year¹¹. Clearly, the PPH R&D landscape will need greater investment to support the development of devices which are fit-for-purpose in low-resource settings and are adequately tested to support their use and widespread roll-out. Given their potential, achieving this will be critical to turning the tide on maternal deaths from PPH and driving progress forward to meet 2030 targets.

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