1 **TITLE: EFFECTIVENESS OF UTERINE TAMPONADE DEVICES FOR REFRACTORY POSTPARTUM**

2 **HAEMORRHAGE AFTER VAGINAL BIRTH: A SYSTEMATIC REVIEW**

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4 **SHORT TITLE: UTERINE TAMPONADE DEVICES FOR PPH AFTER VAGINAL BIRTH**

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24   **ABSTRACT**

25   **Objectives:** to evaluate the effectiveness of uterine tamponade devices for atonic refractory

26   postpartum haemorrhage (PPH) after vaginal birth, and the effect of including uterine tamponade

27   devices in institutional protocols.

28   **Search strategy:** databases in PubMed, EMBASE, CINAHL, LILACS and POPLINE.

29   **Study selection:** randomised and non-randomised comparative studies.

30   **Outcomes:** composite outcome including surgical interventions (artery ligations, uterine

31   compressive sutures or hysterectomy) or maternal death, and hysterectomy.

32   **Results:** all four included studies were at high risk of bias. The certainty of evidence rated as very low

33   to low. One randomised study measured the effect of the the condom-catheter balloon compared to

34   standard care and found unclear results for the composite outcome (RR 2.33, 95%CI 0.76-7.14) and

35   hysterectomy (RR 4.14, 95%CI 0.48-35.93). Three comparative studies assessed the effect of

36   including UBTs in institutional protocols. A stepped-wedge study suggested an increase in the

37   composite outcome (RR 4.08, 95%CI 1.07-15.58), and unclear results for hysterectomy (RR 4.38, 95%

38   CI 0.47-41.09) with the use of the condom-catheter or surgical glove balloon. One non-randomised

39   study showed unclear effects on the composite outcome (RR 0.33, 95%CI 0.11-1.03) and

40   hysterectomy (RR 0.49, 95%CI 0.04-5.38) after the inclusion of Bakri balloon. The second non-

41   randomised study found unclear effects on the composite outcome (RR 0.95, 95%CI 0.32-2.81) and

42   hysterectomy (RR 1.84, 95%CI 0.44-7.69) after the inclusion of Ebb or Bakri balloon.

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43   **Conclusions:** the effect of uterine tamponade devices for the management of atonic refractory PPH

44   after vaginal delivery is unclear, as is the role of the type of device and the setting.

45   **TWEETABLE ABSTRACT**

46   Unclear effects of uterine tamponade devices and its inclusion in institutional protocols for atonic

47   refractory PPH after vaginal delivery.

51   **KEY WORDS**

52   Maternal death, Postpartum haemorrhage, Uterine atony, Vaginal delivery, Bakri Balloon, Condom

53   UBT, Hysterectomy

Introduction

Haemorrhage continues to be the largest direct cause of maternal death, accounting for 661,000 deaths worldwide between 2003 and 2009.[1] Most of these deaths occur during the immediate postpartum period and are due to uterine atony, a condition characterized by the failure of the uterus to contract adequately after the delivery of the placenta.[2]

The majority of women with postpartum haemorrhage (PPH) respond well to first line interventions (uterotonics, uterine massage, tranexamic acid). However, 10% to 20% are unresponsive to these interventions – a subgroup (denoted as "refractory PPH") where most of the PPH-related morbidity and mortality are concentrated.[3] Between one-third and one-half of refractory PPH cases are due to uterine atony. Laparotomy for compressive sutures, ligation of uterine blood supply or hysterectomy are frequently needed to prevent deaths among these women.[4,5] Embolization of uterine arteries by interventional radiology is also an option, although availability in low resource settings is very limited.[2]

Effective non-surgical interventions to manage refractory PPH are critical to avoid surgical treatment and to provide treatment in settings in which surgical treatment is not available. Surgical interventions are associated with increased risk of severe morbidity and mortality, and are not widely available in low-resource settings. The non-surgical interventions currently recommended by the World Health Organization (WHO) for the treatment of refractory PPH due to uterine atony include: manual compressive measures (bimanual uterine compression and external aortic compression), uterine balloon tamponade (UBT), and a second dose of tranexamic acid.[2,6]2,6

Description of the intervention

Under the umbrella of uterine tamponade devices for treating refractory PPH, two categories were considered: uterine balloon tamponade (UBT) devices and uterine suction tamponade (UST) devices. Briefly, UBTs consist of inserting a rubber, silicone or plastic balloon into the uterine cavity, and

78   inflating the balloon with a sterile liquid.[7] The inflated balloon exerts outward pressure on the

79   uterus, achieving a tamponade effect to prevent further bleeding.[8] The UBT can be administered

80   using either improvised or purpose-designed devices.[9] Improvised devices encompass balloon

81   catheters designed for other purposes and used off-label to treat PPH (i.e. the Sengstake-Blakemore

82   tube, the Rusch balloon, the Foley catheter), as well as those based on the use of condoms and

83   surgical gloves attached to Foley or other catheters. Purpose-designed UBTs for PPH treatment are

84   the Bakri® balloon, the EBB® tamponade system (Belfort-Dildy), the Ellavi balloon (by Sinapi

85   Biomedical), and the BT-Cath® balloon.[2,7,10,11]

86   More recently, a novel type of device that uses vacuum force to retract the uterus has been

87   proposed as an alternative to the UBT.[12] Such USTs could be considered a physiologically plausible

88   alternative for the management of unresponsive PPH, as the mechanism of action mimics

89   physiologic uterine retraction. Similar to UBT, there are UST purpose-designed and improvised

90   devices.[8,13]

91   ***Why it is important to do this review***

92   The previous WHO recommendation on UBT was based on case series and studies with no control

93   population, leading to a conditional recommendation. This conditional recommendation does not

94   support widespread application of UBT in all clinical situations. Since the WHO recommendation was

95   published, several additional studies have been reported, including randomised controlled trials

96   (RCTs). Given the importance of UBT as a potential life-saving intervention and the popularity of the

97   intervention globally, it is relevant to systematically review all data available to-date, including the

98   findings of these newer studies.

99   The proliferation of UBT devices over the years, with variable rates of success in terms of reduction

100 of PPH-related morbidity, demands a careful assessment of reported tamponade devices to

101 determine their comparative effectiveness and safety. We undertook the present systematic review

102   aiming to address two key objectives: *1)* to evaluate the clinical effectiveness and safety of different

103   uterine tamponade devices used for treatment of atonic refractory PPH following vaginal birth,

104   compared to any non-surgical intervention (e.g. pharmacological and mechanical treatments)

105   administrated for the treatment of PPH; and *2)* to evaluate the effect of including uterine

106   tamponade devices in an institutional protocol for the management of refractory PPH following

107   vaginal birth.

108   **Methods**

109   This systematic review was conducted following a protocol specifically designed for this purpose and

110   reported according to the recommendations of the PRISMA statement (**Table S1**). The protocol was

111   registered in PROSPERO (CRD42019120486).

112   *Selection of studies*

113   For the first objective, eligible studies were randomised or non-randomised studies that evaluated

114   the effectiveness of a uterine tamponade device versus standard care, in women who developed

115   atonic refractory PPH after vaginal birth (individual level interventions). For the second objective,

116   randomised and non-randomised studies with a control group or period that evaluated the effect of

117   including uterine tamponade devices in institutional protocols for the treatment of refractory PPH,

118   compared to the use of protocols without tamponade devices (facility-level intervention) were

119   included. Abstracts were eligible if sufficient data were reported.

120   *Outcomes*

121   Primary outcomes were: (a) a composite outcome including surgical interventions (laparotomy for

122   artery ligations, uterine compressive sutures or hysterectomy) or maternal death, and (b)

123   hysterectomy.

124   Secondary outcomes were: conservative surgical interventions (compressive sutures and/or artery

125   ligations), maternal death, shock, coagulopathy, organ dysfunction, blood transfusion, transfer to

126   higher level of care, women's sense of wellbeing, acceptability of and satisfaction with the

127   intervention, initiation of breastfeeding, and other adverse effects.

128   The selected outcomes are consistent with those suggested by the COS (Core Outcome Set)

129   initiative.[14] We excluded studies that did not report any of the outcomes previously listed.

130   *Search strategy*

131   The search strategy was developed with the assistance of a librarian experienced in electronic search

132   strategies for systematic reviews (Appendix S1).

133   The search was run from inception to October 2019 in the following electronic databases: PubMed,

134   EMBASE, CINAHL, LILACS, POPLINE. The search was complemented by reviewing the references of all

135   articles selected for full-text reading, and by looking for unpublished studies through contacts with

136   investigators who are experts in the field. There were no language restrictions. We sought out

137   translations if studies were not reported in English, French, and Spanish (languages spoken by

138   reviewers). If translations were not found, then language restrictions were applied.

139   *Data extraction and synthesis*

140   Citations were downloaded from the reference manager RIS to Covidence[15], a web-based platform

141   used to support the conduct of systematic reviews. Titles and abstracts of all imported citations

142   were screened by at least two reviewers using Covidence, and those that were potentially eligible

143   were selected for full-text review. At least two independent reviewers performed the process of

144   study selection and data extraction (MW, VP, GC). A form specifically designed for this review was

145   used to extract data from included studies. Disagreements were discussed until consensus was

146   reached and if required, a third reviewer was consulted. Where information from an article was not

147   clear, authors were contacted to provide additional details.

148   *Risk of bias assessment*

149   Two reviewers assessed the risk of bias by using the 'Risk of bias' tool described in the *Cochrane*

150   *Handbook for Systematic Reviews of Interventions* for randomised studies, and the ROBINS-I tool

151   (Risk of Bias in Non-Randomised Studies of Interventions) for non−randomised studies.[16,17] For

152   randomised studies, random sequence generation and allocation concealment were assessed at the

153   study level. The following were assessed at the outcome level: blinding of participants and

154   personnel, and outcome assessors; incomplete outcome data, selective reporting; other bias. Quality

155   assessment criteria used to assess non-randomised studies were: bias due to confounding, bias in

156   selection of participants into the study, bias in classification of interventions, bias due to deviations

157   from intended interventions, bias due to missing data, bias in measurement of outcomes, bias in

158   selection of the reported result and overall bias. We assessed the risk of bias for each criterion as

159   'low risk', 'high risk', and 'unclear risk' (**Table S2** and **Table S3**).

160   In addition, the Grading of Recommendations Assessment, Development and Evaluation (GRADE)

161   Criteria[18] were used to assess the certainty of evidence for the outcomes prioritized in this review.

162   The overall certainty in the evidence was classified in one of four categories: high, moderate, low or

163   very low.

164   *Strategy for analysis and data synthesis*

165   While the studies assessing individual-level interventions were analysed with the number of all

166   women with PPH after vaginal birth as the denominator, the studies assessing facility-level

167   interventions were analysed with the total number of vaginal births as the denominator. This is

168   because facility-level interventions could have an effect on PPH detection rates. Thus, the most

169   comparable populations between periods or hospitals are all women having vaginal births during the

170   study periods.

171   As all variables from which data could be obtained were found to be dichotomous, we calculated risk

172   ratios (RR) with 95% confidence intervals (CI). Two out of four included studies reported outcomes

173   using a different denominator or measure of effect. Whenever possible, we conducted additional

174   pre-specified subgroup analyses by type of device (purpose-designed and improvised devices) and

175   by setting: low- and middle-income countries (LMICs) and high-income countries (HICs). The

176   summary statistics for each of the included studies were reported in tables. Given the variations in

177   denominators and measures of effect, the summary table includes effect estimates reported by the

178   authors of each study. Meta-analyses were not possible due to high degrees of heterogeneity.

179   Cochrane's Review Manager 5.3[19] software was used to conduct statistical analyses.

180   **Results**

181   *Description of studies*

182   The search strategy yielded a total of 9,430 citations. After screening titles and abstracts, the

183   reviewers selected 621 citations for full-text review. Twenty-one studies were eligible according to

184   our selection criteria. Four out of 21 compatible citations were ultimately included.[20-23] (**Figure S1**)

185   The excluded studies and the reasons for exclusion are described in **Table S4**. There were no studies

186   assessing the effectiveness of UST devices. Included studies were published between January 2007

187   and October 2019.

188   **Table 1** presents the main characteristics of the four included studies. One study conducted in Benin

189   and Mali assessed the effectiveness of UBT devices for refractory postpartum haemorrhage after

190   vaginal birth by comparing the condom-catheter balloon against standard care.[22] Three studies

191   assessed the effects at the facility-level of including UBT devices as a treatment option for refractory

192   PPH after vaginal birth, including one stepped-wedge cluster RCT conducted in Uganda, Senegal and

193 Egypt introducing condom or glove catheter[20] and two non-randomised studies conducted in France:

194 one comparing outcome rates at the hospital-level before and after introduction of the Bakri balloon

195 [21] and the other comparing outcomes between one perinatal network using the Bakri/ EBB® and one

196 control network[23].

197 To assess the validity of included studies, we rated individual criteria for each study, which were

198 specific for randomised and non-randomised studies. Details of the quality of each individual study

199 are described in **Figure 1** and **Table S5**. Overall, the studies showed a high risk of bias.

200 In concordance with the Cochrane Agency for Healthcare Research and Quality (AHRQ) standards,

201 these studies were rated as low-quality randomised trials. Although the included non-randomised

202 studies were judged as high-to-moderate quality, they carry the biases inherent to their respective

203 study designs.

204 ***Effect of the interventions***

205 1. *Effect of any type of uterine tamponade device vs standard care in women with refractory PPH*

206 **Table 2** shows the effect of any type of UBT device versus no device in women with atonic refractory

207 PPH (individual-level intervention) on primary and secondary outcomes. Only one RCT reported the

208 effect of the use of condom-catheter balloon on these outcomes.[22] There is an unclear risk of

209 surgical interventions or death associated with the use of the condom-catheter balloon plus

210 misoprostol as compared to misoprostol alone (RR 2.33, 95%CI 0.76-7.14). The same RCT[22] reported

211 unclear results with respect to hysterectomy (RR 4.14, 95%CI 0.48-35.93). For the secondary

212 outcomes, the results of this trial are unclear and graded as very low-certainty evidence (risk of

213 conservative surgical interventions (RR 2.07, 0.54-7.88), maternal death (RR 6.21, 95%CI 0.77-49.98),

214 blood transfusions (RR 1.49, 95%CI 0.88-2.51) and transfer to a higher level of care (RR 1.29, 95%CI

215 0.55-3.04).

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216 Subgroup analyses by device or setting were not possible. The included RCT evaluated an

217 randomised device and was conducted in Benin and Mali, two low-income countries.[22]

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219 *2. Effect of including UBTs in institutional protocols vs either a previous period in which the UBT was*

220 *not used or other clinical settings without including UBT.*

221 The effect of including UBT devices in institutional protocols for the treatment of refractory PPH on

222 primary and secondary outcomes are shown in the **Table 3**.

223 The experimental study by Anger *et al.*, which used a stepped-wedge design, suggests a four-fold

224 statistically significant increase in surgical interventions or maternal deaths associated with

225 introducing improvised UBTs (RR 4.08, 95%CI 1.07-15.58).[20] In contrast, two non-randomised studies

226 showed unclear effects after the inclusion of the Bakri balloon (RR 0.33, 95%CI 0.11-1.03) and Bakri/

227 Ebb balloon (RR 0.95, 95%CI 0.32-2.81) on the composite outcome.[20,22]

228 Three studies reported hysterectomy rates and were graded as low-certainty evidence. The Anger *et*

229 *al.* trial used the condom-catheter device and found unclear results (RR 4.38, 95%CI 0.47–41.81), as

230 did both non-randomised studies which assessed purpose-designed UBT (RR 0.49, 95%CI 0.04-5.38

231 and RR 1.84, 95%CI 0.44-7.69, respectively).[21,23]

232 Regarding the subsequent need for conservative surgical interventions (artery ligation, compressive

233 sutures), the RCT (Anger at al.) suggests a statistically significant increase in the risk of additional

234 conservative interventions associated with improvised devices (RR 2.82 95%CI1.03 – 7.71)[20], while

235 the non-randomised studies evaluating purpose-designed devices showed unclear results (RR 0.29,

236 95% CI 0.08–1.06[21,23] and RR 0.21, 95% CI 0.02–1.82[23]). For other secondary outcomes, the RCT

237 assessing the condon-catheter device found unclear results with respect to maternal deaths (RR

238 2.23, 95%CI 0.35–14.07), blood transfusion (RR 1.24, 95%CI 0.86–1.80) and transfer to a higher level

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239   of care (RR 3.05, 95%CI 0.79–11.70) [20]. Neither of the non-radomised studies assessing purpose-

240   designed UBTs provided additional data regarding maternal death; no maternal deaths due to PPH

241   were reported in the Laas study and the risk of maternal death after vaginal delivery was not

242   assessed in the Revert *et al.* study. Laas *et al.* reported unclear results on blood transfusions (RR 1.43

243   95%CI 0.76–2.71). Neither of the non-randomised studies reported the effect of a purpose-designed

244   device on transfer to a higher level of care.

245   The study by Revert *et al.* considered artery embolization in their primary outcome (a composite

246   outcome of surgical interventions), and the authors conducted the analysis and interpretation of the

247   results on that basis.[23] As we did not include invasive non-surgical interventions among the surgical

248   interventions in our primary outcome, we analysed the Revert *et al.* study data excluding women

249   receiving such procedure. The results of this study, including artery embolization in the composite

250   outcome as reported by the authors, shows a statistically significant reduction in the surgical

251   interventions and deaths associated with the use of UBTs (adjusted RR 0.14, 95%CI 0.08- 0.27), while

252   unclear results were found when excluding artery embolization (RR 0.95, 0.32-2.81).

253   It was not possible to analyse effects by device or setting. The Anger *et al.* trial evaluating an

254   improvised device was conducted in LMICs, while the non-randomised studies evaluating purpose-

255   designed devices were conducted in HICs.

256   Some of the outcomes of interest, such as blood loss, shock, coagulopathy, organ dysfunction,

257   women's sense of wellbeing, acceptability and satisfaction with the intervention, and breastfeeding

258   were not reported in the included studies.

259   **Quality of the evidence according to GRADE assessment**

260   **Tables 2 and 3** shows details on the quality of evidence according to GRADE criteria for the two

261   comparisons of interest. Overall, the assessment showed a low to very low certainty of the evidence

262   for all outcomes. For the first comparison—any type of uterine tamponade devices compared to no

263   devices—we found low quality of evidence for the composite outcome and very low quality for

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264   hysterectomy in the study evaluating use of UBT at the individual level. Similar judgements were

265   obtained (low quality of evidence for the composite outcome and very low quality for secondary

266   outcomes) for the second comparison—inclusion of uterine tamponade devices in institutional

267   protocols—when evaluating purpose-designed devices at the facility-level, independent of the study

268   design. The quality of evidence was low to very low for all secondary outcomes: hysterectomy,

269   surgical interventions, maternal death, blood transfusion and transfer to a higher level of care. These

270   results were consistent across different study designs (randomised and non-randomised) and level of

271   intervention (individual or facility).

272   **Discussion**

273   *Summary of main results*

274   Four studies assessing the effectiveness and safety of UBTs for the treatment of atonic refractory

275   PPH after vaginal delivery were included. The evidence from the RCT[22] assessing the effect of

276   improvised UBT devices in women with refractory PPH showed unclear results in subsequent surgical

277   interventions, maternal deaths or hysterectomy alone when compared with standard care. Three

278   studies assessing the effect of including UBTs in an institutional protocol for the management of PPH

279   showed conflicting results. The RCT[20] suggested an increase in subsequent surgical interventions and

280   maternal deaths, and unclear results in the risk of hysterectomy associated with the use of the

281   condom-catheter or surgical glove balloon. The two non-randomised studies assessing the inclusion

282   of purpose-designed balloons in institutional protocols found an unclear effect on the composite

283   outcome and hysterectomy[21,23]. While the RCTs evaluated the improvised UBTs in LMICs, the non-

284   randomised studies assessed purpose-designed UBTs and were conducted in HICs. Therefore, it was

285   not possible to disentangle the effect by type of device or by setting.

286   *Overall completeness, quality of the studies and quality of the evidence*

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287 After a detailed quality assessment of the studies included in this systematic review, we identified

288 substantive methodological flaws in both RCTs and determined they had a 'high' risk of bias.

289 Included non-randomised studies were judged as high-to-moderate quality but have the biases

290 inherent to their respective study designs. Consequently, for the systematic review primary

291 outcomes, the certainty of the evidence was graded as low to very low due to study limitations and

292 because of imprecision.

293 *Factors that may be determinants of the effect of UBT*

294 <u>Improvised UBTs versus purpose-designed UBTs</u>

295 One randomised trial comparing the condom-catheter to Bakri balloon reported longer time to

296 control bleeding with condom-catheter balloon but no difference in substantive outcomes.[24] In

297 addition, further analysis suggests that implementation fidelity and quality may influence findings.

298 For example, the studies using improvised-devices in LMICs reported delays in treatment

299 administration. The Dumont *et al.* trial[22] reported that the condom-catheter balloon was inserted

300 within 30 minutes of PPH diagnosis in only 58% of cases. Furthermore, the stepped-wedge cluster

301 RCT by Anger *et al*. mentioned that providers reported a problem with the condom-catheter balloon

302 in 52% of the cases.

303 <u>The setting</u>

304 The effective management of refractory PPH requires an expeditious stepwise approach, in which

305 the availability of resources and a well-operating health system are essential.[25] It is plausible that in

306 settings where the identification of PPH and subsequent quality of care is more likely to be

307 substandard, the effect of the UBT may be different from in settings with good availability of

308 resources and high quality of care. The Dumont *et al*. trial reported that frequent delays in the

309 diagnosis and treatment of uterine atony were observed, with a high proportion of women receiving

310 a late injection of oxytocin in the first response.[22] Similarly, the stepped-wedge cluster RCT by Anger

311   *et al.*[20] reported that blood shortages were a problem for almost half of PPH-related deaths in the

312   study, including some cases in which, despite bleeding stopping after administration of the UBT, the

313   woman did not recover because timely blood replacement was unavailable. The authors suggested,

314   "interventions such as UBT may have limited effectiveness in improving maternal outcomes when

315   introduced into resource-constrained health systems with unreliable access to other essential

316   components of emergency care".[20]

317   Another potentially important aspect related to the setting has to do with whether the UBT

318   procedure is performed in the delivery room or in the surgical theatre. Typically, in some HICs like

319   UK and US, the procedure is conducted in the surgical theatre, following exploration of the uterine

320   cavity to exclude trauma as the cause of the bleeding. Conversely, in LMICs the procedure is usually

321   performed in the delivery room, frequently without exploration of the uterine cavity. On one hand,

322   performing the procedure in the surgical theatre after excluding other causes may avoid applying the

323   UBT in cases with no uterine atony, thus avoiding delays to administer the correct treatment.

324   Additionally, if the UBT fails, surgical treatment can be started without delay. On the other hand, in

325   low-resource settings, such requirements may contribute to delay of the UBT procedure. In the

326   Dumont trial, a large proportion of the UBT procedures were performed in the operating theatre of

327   referral hospitals. The authors reported "the recurring unavailability of the theatre had an important

328   consequence in the delays for the experimental group".[22]

329   *Strengths and limitations*

330   The strengths of this systematic review include following rigorous Cochrane methods and the

331   PRISMA protocol for reporting. The broad search strategy captured a large number of published and

332   unpublished studies. To assess effectiveness, we tightly restricted eligibility to studies that selected

333   women with suspected uterine atony and refractory PPH, and reported additional surgical

334   interventions or maternal death. We included all types of studies that compared the effectiveness of

335   UBT with medical treatment and local standard of care. Case reports were not included to assess

336   effectiveness; given that this systematic review will inform clinical and policy decision-making,

337   comparative effectiveness evidence is required. Although the inclusion timeframe for this review

338   was intentionally long in order to identify a wide range of devices reported in the literature, most

339   included studies were published recently. As the included studies used different types of UBT

340   devices and were conducted in different countries, effort was made to highlight these distinctions

341   throughout the analysis.

342   Our review also has some limitations mainly derived from the scarcity and kind of information

343   reported in articles. We found very few studies reporting the effect of UBT in atonic refractory PPH

344   after vaginal delivery. We excluded 10 analytical studies because outcomes were measured in all

345   births[26-35], without disaggregating data according to mode of delivery (**Table S4**), with a quarter to

346   half of included cases ending in caesarean sections. Six studies were excluded due to: insufficient

347   data[36], involved women having a caesarean section[37], the intervention being administrated as part of

348   a package[38], UBT being administrated as a first line treatment for PPH[39], the outcomes reported

349   differing from the prioritized outcomes in this systematic review[40,41] or involving the comparison of

350   two different types of UBT[24]. It was possible to extract data after vaginal birth in only two studies.[21,23]

351   Finally, the inability to pool risk estimates due to the heterogeneity in the study designs should be

352   noted. The heterogeneity in the estimation of blood loss and the definition of refractory PPH is also a

353   limitation of this study.

354   *Agreements and disagreements with other reviews*

355   In 2020, Suarez *et al.* published a comprehensive systematic review, including RCTs , non-

356   randomised studies of interventions, and case series that reported on the efficacy, effectiveness,

357   and/or safety of UBT in women with PPH due to a variety PPH aetiologies, after vaginal or caesarean

358   delivery.[42] The main outcome was the UBT success – defined as bleeding arrested without maternal

359   death or additional surgical or radiological interventions in women in which the UBT was placed. This

360   systematic review differs from Suarez *et al.* in that we did not include case report studies, given

361   their key limitation of not having a comparison group. Additionally, we restricted our focus to atonic

362   refractory PPH after vaginal delivery only. Both reviews acknowledge the conflicting evidence and

363   unclear results from RCTs compared to non-randomised studies.

364   **CONCLUSION**

365   According to the body of evidence currently available, the effect of UBT for the management of

366   atonic refractory PPH after vaginal delivery is unclear. Whether the type of device or the setting are

367   important factors associated with UBTs' effect is unknown.

368   *Implications for practice*

369   There is uncertainty about the effectiveness and safety of UBT for the treatment of women with

370   refractory PPH after vaginal delivery in low resource settings with unreliable access to good quality

371   PPH care. Our view is that UBT should be considered for routine refractory PPH care only in settings

372   where birth attendants are appropriately trained to use tamponade devices and manage PPH, where

373   access to surgical interventions and blood products are available if needed, where differential

374   diagnosis of other causes of PPH can be performed, and where the resources required for PPH

375   management are routinely available and maternal status can be appropriately monitored.

376   *Implications for research*

377   In low-resource settings not meeting the criteria mentioned above, the efficacy and safety of UBT for

378   the treatment of women with refractory PPH after vaginal delivery should be evaluated through

379   good quality RCTs. In well-resourced settings, it is a priority to assess the comparative efficacy of

380   different purpose-designed UBTs against improvised devices. The effectiveness of UST devices

381   should also be assessed though high-quality RCTs.

382

383   **FUNDING**

387

391 **AUTHOR CONTRIBUTIONS**

392 Study conceptualization: FA and MW. FA, MW, GC, AC and VP contributed to drafting the protocol.

393 MW, GC and VP selected studies for inclusion and extracted data. DC designed and ran the search

394 strategy. DC and PVa locacated all full texts. AC, AB and VP conducted the quality assessements. AC

395 and VP conducted data analysis. FA, MW, VP, AC and GC contributed to drafting the review. VP, MW,

396 AC, GC, KB, CD, MG, JH, OTO, VPa, AB, DC and FA reviewed, provided comments and edits, and

397 approved the manuscript.

398

399 **CONFLICTS OF INTERESTS**

400 VP, MW, FA, AC, GC, CD, MG, OTO, VPa, AB, DC have no conflicts of interest. GJH initiated the use of

401 the Levin suction catheter as a uterine suction tamponade device. He did not participate in decisions

402 regarding inclusion of reports on the Levin tube method in the review. KB has been participating in a

403 European expert meeting Challenges in the Current Management of Postpartum Haemorrhage (PPH)

404 organized by CSL Behring.

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Table 1. Main characteristics of included studies for the evaluation of effectiveness

Research question	Study design	Study and year	Country	Sample size	Inclusion criteria	Intervention	Control	Main Outcome
Q1. Any type of uterine tamponade device vs standard care (individual-level intervention)	Randomised	Dumont *et al.* 2017	Benin and Mali	116	PPH due to a suspected uterine atony unresponsive to first line treatment subsequent to vaginal delivery	condom-catheter balloon + misoprostol	Misoprostol	Surgical intervention (arterial ligatures, uterine compressive sutures, hysterectomy) or death before discharge
	Randomised	Anger *et al.* 2019	Uganda, Senegal and Egypt	59,765	Vaginal delivery; delivery at a study hospital or referral to a study hospital for PPH after delivery elsewhere	condom-catheter balloon or surgical glove	Standard care	Maternal death or invasive procedures
Q2. Inclusion of UBT in an institutional protocol for the management of PPH compared to protocols without UBT (facility-level intervention)	Non-randomised	Laas *et al.* 2012	France	23,863	PPH due to uterine atony that is unresponsive to sulprostone after a vaginal delivery or caesarean section[a]	Bakri balloon	Oxytocin and sulprostone	Arterial embolization, conservative surgical procedures (artery ligations and/or uterine compression sutures), and hysterectomy
	Non-randomised	Revert *et al.* 2018	France	73,529	Women with PPH from uterine atony unresponsive to sulprostone after a vaginal delivery or a caesarean section[a]	Bakri or ebb balloon	Medical treatment	Arterial embolization or surgery (pelvic vessel ligation or hysterectomy)

Table 2: Summary of findings for the first comparison: Intrauterine balloon tamponade compared to normal care for the management of refractory PPH (Individual-level intervention)

Outcomes	Study	Relative effect (95% CI)	Certainty of the evidence
Composite outcome (Surgical interventions and/or death)	Dumont *et al.* 2017	**RR 2.33 (0.79 to 7.14)**	⊕⊕◯◯ LOW [a,b]
Hysterectomy to control bleeding	Dumont *et al.* 2017	**RR 4.14 (0.48 to 35.93)**	⊕◯◯◯ VERY LOW [a,d]
Conservative surgical interventions (BL and/or, AL)	Dumont *et al.* 2017	**RR 2.07 (0.54 to 7.88)**	⊕⊕◯◯ LOW [a,b]
Maternal death due to bleeding	Dumont *et al.* 2017	**RR 6.21 (0.77 to 49.98)**	⊕◯◯◯ VERY LOW [a,d]
Blood transfusion	Dumont *et al.* 2017	**RR 1.49 (0.88 to 2.51)**	⊕⊕◯◯ LOW [a,b]
Transfer to higher level of care	Dumont *et al.* 2017	**RR 1.29 (0.55 to 3.04)**	⊕⊕◯◯ LOW [a,b]

[a]**The risk in the intervention group** is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio. **GRADES of evidence: High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect. **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. **Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. **Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. Explanations: a. Downgraded one level because high risk of bias on blinding, other bias (imbalanced baseline) and unclear allocation concealment; b. Downgraded one level because of its wide confidence interval; c. Downgraded one level because high risk of bias on blinding, unclear risk of bias on random sequence generation and on selective reporting; d. Downgraded two levels because of its too wide confidence interval; e. Downgraded two levels because the included studies are non-randomised studies

Table 3: Summary of findings for the second comparison: Use of Intrauterine balloon tamponade as part of an institutional protocol for the management of refractory PPH (facility-level intervention)

Outcome	Study	Effect estimate (95% CI)		Certainty of the evidence (for the effect estimate among all vaginal births)
		All vaginal births as denominator	Reported by study authors	
Composite outcome (Surgical interventions and/or death)	Anger *et al.* 2019	RR[a] 4.08 (1.07 to 15.58)	RR[a] 4.08 (1.07 to 15.58)	⊕⊕○○ LOW[d,e]
	Laas *et al.* 2012	RR 0.33 (0.11 to 1.03)	Not reported	⊕⊕○○ LOW[g]
	Revert *et al.* 2018	RR[b] 0.95 (0.32 to 2.81)	Not reported	⊕⊕○○ LOW[g]
Hysterectomy	Anger *et al.* 2019	RR[a] 4.38 (0.47 to 41.09)	RR[a] 4.38 (0.47–41.09)	⊕○○○ VERY LOW[e,g]
	Laas *et al.* 2012	RR 0.49 (0.04 to 5.38)	OR[c] 0.44 (0.04–4.91)	⊕○○○ VERY LOW[d,g]
	Revert *et al.* 2018	RR 1.84 (0.44 to 7.69)	Not reported	⊕○○○ VERY LOW[d,g]
Conservative surgical interventions (BL, AL)	Anger *et al.* 2019	RR 2.82 (1.03 to 7.71)	RR 2.82 (1.03 to 7.71)	⊕⊕○○ LOW[d,e]
	Laas *et al.* 2012	RR 0.29 (0.08 to 1.06)	OR[c] 0.26 (0.07 to 0.95)	⊕⊕○○ LOW[g]
	Revert *et al.* 2018	RR 0.21 (0.02 to 1.82)	Not reported	⊕○○○ VERY LOW[d,g]
Maternal death	Anger *et al.* 2019	RR[a] 2.23 (0.35 to 14.07)	RR[a] 2.23 (0.35 to 14.07)	⊕○○○ VERY LOW[e,f]
	Laas *et al.* 2012	No events	No events	-
	Revert *et al.* 2018	Cannot estimate	Not reported	-
Blood transfusion	Anger *et al.* 2019	RR[a] 1.24 (0.86 to 1.80)	RR[a] 1.24 (0.86 to 1.80)	⊕⊕○○ LOW[d,e]
	Laas *et al.* 2012	RR 1.43 (0.76 to 2.71)	OR[c] 1.31 (0.67 to 2.56)	⊕○○○ VERY LOW[d,g]
	Revert *et al.* 2018	Not reported	Not reported	-
Transfer to higher level of care	Anger *et al.* 2019	RR[a] 3.05 (0.79 to 11.70)	RR[a] 3.05 (0.79 to 11.70)	⊕○○○ VERY LOW[e,f]
	Laas *et al.* 2012	Not reported	Not reported	-
	Revert *et al.* 2018	Not reported	Not reported	-

CI: Confidence interval; **RR:** Risk ratio; **GRADE Working Group grades of evidence: High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect. **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. **Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a] Adjusted for study design; [b] In contrast to the composite outcome reported by the study authors, we did not include artery embolization in the composite outcome for this review; [c] Study authors used the number of women who required intravenous sulprostone as denominator; [d] Downgraded one level due toits wide confidence interval; [e] Downgraded one level due to high risk of bias on blinding, and unclear risk of bias on random sequence generation and on selective reporting; [f] Downgraded two levels due to its wide confidence interval; [g] Downgraded two levels because the included studies are non-randomised studies.