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Every minute counts: a network meta-analysis comparing the effect of prophylactic endovascular procedures in abnormal placentation

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Abstract

Background Preventing postpartum haemorrhage remains a high priority worldwide. We aimed to provide all available evidence comparing maternal and neonatal outcomes of different prophylactic endovascular procedures in patients with abnormal placentation.

Methods Pubmed, Embase and ClinicalTrials.gov databases were searched from inception to Nov, 2024, using relevant key words. Studies comparing outcomes of women undergoing or not prophylactic endovascular procedures in planned cesarean delivery in patients with antenatally suspected or confirmed PAS, placenta previa or both were included. An arm-based random effect frequentist network meta-analysis was performed. All available maternal and neonatal outcomes were evaluated.

Results Three randomized controlled trials and 59 observational studies were eligible reporting on 6973 women (42.9% did not undergo any endovascular procedure, 26.7% underwent aortic balloon occlusion, REBOA, 16.6%, internal iliac balloon occlusion, PBO-IIA, 5.8%, common iliac artery occlusion, PBO-CIA, placement, and 7.8% underwent uterine artery embolization, UAE). The pooled network analysis showed that all prophylactic endovascular procedures were associated with reduced perioperative blood loss, with proximal balloon occlusion (REBOA) having the strongest effect (SMD −1.80 L, 95%CI −2.38;-1.21; $I^2 = 97.2\%$). Also, peripartum hysterectomy rates were significantly lower in women undergoing prophylactic UAE and REBOA compared to the control group; moreover, patients with placenta previa without any prophylactic endovascular procedure had a 4 to fivefold increased risk of peripartum hysterectomy compared to the REBOA group ($I^2 = 20.6\%$). REBOA was associated with a significant decrease in massive transfusion rates ($I^2 = 0\%$), surgery-related complications ($I^2 = 0\%$), ICU admissions ($I^2 = 40.3\%$), and units of red blood cells transfused ($I^2 = 92.8\%$), compared to PBO-IIA and control groups. The control group versus women undergoing prophylactic UAE showed a significant increase in total operative time ($I^2 = 96.5\%$) and Clavien-Dindo grade IV post-operative complications ($I^2 = 26\%$), compared to REBOA. All prophylactic endovascular procedures had a comparable risk ratio in terms of units of platelets transfused, maternal mortality, and use of additional post-operative bilateral

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uterine artery embolization among the treatment groups. As for neonatal outcomes, no significant differences were detected.

Conclusions Although the preponderance of observational studies suggests caution in interpreting the results of this meta-analysis, our findings suggest that prophylactic endovascular interventional procedures, particularly aortic balloon occlusion, may substantially improve clinical outcomes in women with PAS, placenta previa or both.

PROSPERO registration number CRD4202457398.

Keywords Postpartum hemorrhage, Aortic balloon occlusion, Embolization, Placenta previa, Placenta accreta spectrum disorders, Abnormal placentation

Background

Postpartum haemorrhage (PPH) remains the leading cause of maternal mortality in low-income countries and accounts for nearly a quarter of all maternal deaths worldwide [1]. Over the past two decades, the evolving landscape of pregnancy risk factors and care has presented gynecologists with a growing number of complex scenarios. Placental disorders such as placenta previa and placenta accreta spectrum disorders (PAS) are a major cause of massive, life-threatening peripartum haemorrhage, accounting for more than half of peripartum hysterectomies performed as a definitive strategy to secure hemostasis [2, 3]. An increase in caesarean deliveries due to maternal request, the growing number of women seeking assisted reproductive techniques, and the obstetrical medicolegal environment that may influence subjective indications, are likely associated with and increased incidence of abnormal placentation, especially in high-income countries [4–9].

Given the importance of this condition, endovascular interventional strategies for bleeding control have been on the rise along with the evolution of multidisciplinary team-based care for women with abnormal placentation. Despite inconclusive literature about their safety and effectiveness to reduce morbidity and mortality, clinical outcomes have improved over the last two decades.

Systematic reviews and meta-analyses showed that endovascular interventional techniques are associated with less intraoperative blood loss, need for transfusion and lower rates of peripartum hysterectomy [10, 11]. At present, there is no conclusive evidence to recommend a specific endovascular intervention for prophylactic PPH control. It has been hypothesized that arterial embolization or occlusive balloons may reduce uterine blood flow. However, due to the extensive collateral blood supply to the uterus, embolization or balloon occlusion placed at distal levels (common iliac arteries, internal iliac arteries, or uterine arteries) may not be as effective as in the abdominal aorta. Although the resuscitative endovascular balloon occlusion of the Aorta (REBOA)'s primary use was to treat noncompressible torso haemorrhage in trauma surgery [11, 12], emerging applications in obstetrics show that prophylactic, more proximal occlusion (infrarenal abdominal aorta, Zone 3), is likely to be the most effective strategy in preventing catastrophic PPH in patients with PAS by reducing blood loss volume, blood transfusion, peripartum hysterectomy rate, operative time, postoperative hospitalization, and morbidity [13–19].

However, a comprehensive and updated quantitative analysis assessing the safety and effectiveness of these approaches in patients with placental disorders (including placenta previa) is lacking and further evidence is needed to support clinical decision making.

This study aims to provide all available evidence from randomized controlled studies (RCTs) and observational studies comparing maternal and neonatal outcomes of different prophylactic endovascular procedures in patients with abnormal placentation, including PAS and placenta previa.

Methods

The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD4202457398). The current network meta-analysis is presented in agreement with the Preferred Reporting Items for Systematic Reviews and Network Meta-Analyses (PRISMA-NMA) and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines [20]. Because this study was based on previous research, ethical approval and patient consent were not required.

Eligibility criteria, information sources, search strategy

Two reviewers (GBNV and NS) systematically searched Pubmed, Embase and Clinicaltrials.gov databases from inception to Nov. 2024, using the following combined key words ("intra-aortic balloon") OR ("aortic occlusion") OR ("endovascular procedures") OR ("uterine artery embolization") AND ("obstetric"). Search strategies are listed in Supplemental file 1. A manual search was also performed using references from key articles and previous meta-analysis.

Study selection

Randomized and non-RCTs comparing maternal and neonatal outcomes of women undergoing or not prophylactic endovascular procedures for preventing PPH in patients with antenatally suspected or confirmed PAS, placenta previa or both, were considered eligible. The term PAS refers to the entire spectrum of conditions including accreta (trophoblastic attachment to the myometrium without intervening decidua), increta (trophoblast invading the myometrium), percreta (trophoblast invading the myometrium beyond the serosa and into surrounding structures), as well as cases of clinically apparent morbidly adherent placenta (MAP) [3]. Placenta previa is defined as the placenta overlying the endocervical os (to any degree) [3]. Those previa termed "low-lying", which are near (less than 2 cm), but not overlying the os, were also included in the qualitative and quantitative analysis. Prophylactic interventions were defined as pre-emptive vascular access in the common femoral artery for embolization of the uterine arteries (UAE), and preoperative placement of ballon catheters into common iliac arteries (PBO-CIA), internal iliac arteries (PBO-IIA), or abdominal aorta (REBOA). To avoid omission of some studies, our search was performed without restrictions with respect to language. When two or more articles were published by the same institution and used the same data set, articles with the longest follow-up or the largest cohort of patients were included. Case series, case reports, review articles, abstracts, conference proceedings, letters to the editor or commentaries were excluded. Studies including women undergoing emergency caesarean delivery were excluded because the emergency setting was assumed not to provide enough time for a prophylactic intervention. Also, studies including but not quantitatively subgrouping patients undergoing prophylactic placement of occlusive balloons (REBOA, PBO-IIA, PBO-CIA) or embolization for each treatment arm, and studies including only women undergoing peripartum hysterectomy, were all excluded.

Data extraction

The literature was searched and selected by 2 reviewers (GBNV and NS). Full-text articles were identified on the basis of the titles and abstracts, and then carefully evaluated by each reviewer independently. Data extracted from all articles were tabulated, including first author, publication year, country, study design, localization and type of interventions and number of patients, age, parity, risk factors for abnormal placentation, as well as reported maternal and neonatal outcomes (Table 1). Missing data were addressed and clearly defined. No automated tools were used for data extraction. Disagreements were resolved by reaching consensus about relevance and inconsistencies or by discussion with two senior authors (PIC and ABLF).

Primary outcomes were blood loss (estimated or quantitative, L), peripartum hysterectomy rate, and massive transfusion (defined as > 4 PRBC units transfused in less than 24 h) (Supplemental Table 1). Secondary aims were total operative time(skin incision to skin closure), Clavien-Dindo Grade IV post-operative complications (DVT, DIC, hemorragic shock, pulmonary embolism, pulmonary edema, sepsis, pneumonia, cardiac arrest, amniotic embolism), surgery-related complications (bladder injury, ureter injury, bowel entry, bowel deserosation, vesico vaginal fistula, re-laparotomy, abdominal wall hematoma, wound infection), ICU admission rate, number of red blood cell (RBC),platelets(PLT), fresh frozen plasma(FFP) and cryoprecipitates(Cryo) units transfused within 24 h after delivery, maternal mortality and need for additional hemostatic procedures (uterine compression sutures or uterine artery embolization after c-section). For the neonatal side outcomes were: 1 and 5 min Apgar scores, 1 and 5 min Apgar scores less than 7, neonatal intensive care unit admission, neonatal asphyxia and mortality. Because each study did not assess all outcomes of interest, meta-analyses were performed based on a variable number of studies that were related to that outcome. A subgroup analysis according to the type of placental disorder (placenta previa versus accreta) was also carried out. We also aimed to collect data on adverse events related to the studied endovascular procedure, such as occlusive and non occlusive arterial thrombosis, arterial dissection or hematoma, vascular access site complications (e.g., bleeding requiring surgical intervention or open repair, hematoma, arterio-venous fistula formation), injuries from overinflation with either catheter. ischemic complications, renal, gastrointestinal, neurological or limb injuries, catheter migration, catheter malposition, balloon rupture, and uterine necrosis/atrophy.

Assessment of risk of bias

Potential sources of bias were independently assessed by two reviewers (GBNV and NS). Discrepancies were resolved via discussions with two senior assessors (ABLF and PIC). We used the Cochrane's risk of bias (RoB) tool [21, 22] for evaluating the methodological quality of RCTs and observational studies. We evaluated RCTs studies using the following domains: generation of a random sequence, allocation concealment, participant and personnel blinding, blinding in assessment of outcome, inadequate outcome data, selective reporting, and other sources of bias. Each item was judged as low, some concerns, or high risk of bias. The ROBINS-I tool [21] was used for observational studies. The following domains were considered: confounding bias, selection bias,

Table 1 Demographic and clinical data for patients undergoing prophylactic endovascular procedures for PPH prevention and controls, C

Author, year, country Study design	Intervention, n	Known risk factors	Confirmed PAS(IO or HP)	Type of abnormal placentation antepartum known	Outcomes
Zhao et al. [39],2024, CN R	PBO-AO3A, 118 C, 22	Previous CS	+	Placenta previa	BL, HYST, SRC, 1MApgar,5MApgar
He et al. [40], 2023, CN, R	UAE, 20 C, 20	Previous CS	+	Placenta previa	BL, HYST, C-DgradeIV, 1MApgar
Ioschovich et al. [85], 2023, ISRL P	PBO-AO3, 10 C, 11	Previous CS	+	PAS	BL,MassT,RBC(U),FFP(U),Cryo(U),PLT(U),HYST, TOT,SRC,C-DgradeIV,ICUa(n), 1MApgar
Kyozuka et al. [41], 2023, JPN R	PBO-AO3, 13 C, 24	Previous CS	+	PAS	BL,TOT
Ye et al. [42], 2023, CN R	PBO-AO3, 278 C, 86	Previous CS	+	Placenta previa PAS	BL,RBC(U),HYST,TOT,ICUa(n), C-DgradeIV,SRC, 1MApgar,5MApgar, NICUa(n)
Hong et al. [43],2022, CN R	PBO-IIA, 23 C, 35	Previous CS,uterine surgeries	+	PAS	BL, RBC(U), FFP(U),Cryo(U),HYST,AMSH,TOT, SRC, C-DgradeIV,MM, 1MApgar,5MApgar,NM
Liu et al. [44], 2022, CN R	PBO-AO3, 168 C, 106	Previous CS	+	PAS	BL,TOT,ICUa(n), AMSH,HYST, C-DgradeIV,SRC, 1MApgar,5MApgar, NA
Lou et al. [86],2022, CN P	PBO-AO3,30 C, 34	Previous CS,uterine surgeries ART	–	PAS	BL, TOT,AMSH,HYST, C-DgradeIV,SRC, 1MApgar,5MApgar
Riazanova et al. [45],2022, RUS R	PBO-CIA,16 C,12	Previous CS	+	PAS	BL,TOT,HYST,, C-DgradeIV
Wang et al. [46],2022, RUS R	PBO-AO3, 276 C, 554	Previous CS,uterine surgeries,ART		Placenta previa PAS	HYST,SRC
Yin et al. [47], 2022, CN R	PBO-AO3, 68 C, 88	NR	+	PAS	BL,RBC(U), Cryo(U),TOT,, MassT, C-DgradeIV,AMSH,SRC, NICUa(n), ASless1, ASless5,NA
Zhang et al. [48], 2022, CN R	PBO-IIA, 38 C, 96	NR	+	Placenta previa	BL,TOT,ICUa(n)
Zheng et al. [49],2022, CN R	PBO-AO3, 132 C, 132	NR	–	Placenta previa PAS	BL,HYST,SRC, 1MApgar,5MApgar, ASless1, ASless5
Loffe et al. [87], 2021, US P	PBO-AO3, 17 C, 73	Previous CS	+	Placenta previa PAS	BL,MassT,RBC(U),ICUa(n),SRC
Fan et al. [88], 2021, CN P	PBO-IIA, 56 C, 72	Previous CS,uterine surgeries	–	Placenta previa PAS	BL,AMSH, HYST,TOT, 1MApgar,5MApgar,NICUa(n)
Huo et al. [50], 2021, CN R	PBO-AO3, 5 C, 16	Previous CS	–	Placenta previa PAS	BL,HYST,AMSH,RBC(U),PLT(U), 1MApgar,5MApgar
Savukyne et al. [51],2021, LT R	PBO-IIA, 19 C, 47	Previous CS,uterine surgeries,manual removal of the placenta,ART	+	PAS	BL,RBC(U),AMSH,HYST,SRC, 1MApgar,5MApgar
Chen et al. [52],2021, CN R	PBO-IIA, 248 C, 172	Previous CS	–	Placenta previa PAS	BL, MassT,FFP(U),PLT(U),ICUa(n) HYST,SRC, NA, NICUa(n), 1MApgar
Ahmed et al. [53],2020, QAT R	PBO-IIA, 33 C, 34	Previous CS	+	Placenta previa PAS	BL, HYST,SRC,MM
Cho et al. [54],2020, CN R	PBO-IIA, 17 C, 25	Previous CS	+	PAS	BL, HYST, LOS, SRC,MM, 1MApgar,5MApgar
Dai et al. [55],2020, CN R	PBO-IIA, 22 C, 27	Previous CS	+	Placenta previa PAS	BL RBC(U), HYST, AMSH, C-DgradeIV, 1MApgar,5MApgar

Table 1 (continued)

Author, year, country Study design	Intervention, n	Known risk factors	Confirmed PAS(IO or HP)	Type of abnormal placentation antepartum known	Outcomes
Mohr-Sasson et al. [56],2020, ISRL R	UAE, 64 C, 20	Previous CS	–	Placenta previa PAS	BL,TOT,HYST,SRC, C-DgradeIV
Peng et al. [57],2020, CN R	PBO-IIA, 48 C, 56	Previous CS	–	Placenta previa PAS	TOT,BL,HYST,SRC,ICUa(n), 1MApgar,5MApgar
Radaelli et al. [89],2020, ITA P	UAE, 32 C, 44	Previous CS,uterine surgeries, endometriosis	+	Placenta previa	BL,TOT,AMSH,HYST,ICUa(n)
Tokue et al. [58],2020, JPN R	PBO-AO3, 32 PBO-IIA, 28	Previous CS	+	Placenta previa PAS	BL,TOT,HYST,din(U),5MApgar
Yu et al. [36],2020, HK RCT	PBO-IIA, 32 C, 28	Previous CS,ART	+	Placenta previa	BL,TOT,RBC(U),PLT(U),,FFP(U) ,Cryo(U),AMSH,HYST,ICUa(n), SRC,MM, ASless5, NICUa(n)
Yuan et al. [59],2020, CN R	UAE, 28 C, 26	Previous CS	+	PAS	BL,RBC(U),HYST, C-DgradeIV
Zhu et al. [60],2020, CN R	PBO-AO3, 25 C, 23	Previous CS	–	Placenta previa PAS	BL,TOT,HYST,ASless1,ASless5
Chen et al. [37],2020, CN RCT	PBO-IIA, 50 C, 50	Previous CS,uterine surgeries	–	Placenta previa PAS	RBC(U), BL,HYST,SRC,ICUa(n),TOT, C-DgradeIV
Mei et al. [61],2019, CN R	PBO-AO3, 100 PBO-IIA, 74	Previous CS	–	Placenta previa PAS	BL,TOT,AMSH
Peng et al. [62],2019, CN R	PBO-AO3, 100 PBO-CIA, 74	NR	+	Placenta previa PAS	BL,TOT
Wang et al. [63],2019, CN R	UAE, 32 C, 15	Previous CS	+	Placenta previa PAS	HYST,MM,NA
Wei et al. [64],2019, CN R	PBO-AO3, 32 PBO-IIA, 15	NR	+	Placenta previa PAS	TOT,HYST,ICUa(n),AMSH
Zhou et al. [65],2019, CN R	PBO-IIA, 58 C, 25	Previous CS	+	Placenta previa PAS	BL, C-DgradeIV,HYST
Blumenthal et al. [66],2018, US R	PBO-AO3, 16 C, 19	Previous CS,uterine surgeries	–	PAS	BL,ICUa(n), SRC,C-DgradeIV,1MApgar,5MApgar
Dai et al. [67],2018, CN R	PBO-IIA, 20 C, 22	NR	+	Placenta previa	BL,RBC(U), C-DgradeIV,HYST
Duan et al. [68],2018, CN R	PBO-AO3, 22 C, 23	Previous CS,uterine surgeries	+	Placenta previa	TOT, BL,AMSH,HYST,NA
Gulino et al. [90],2018, CN P	PBO-IIA, 16 C, 21	Previous CS,uterine surgeries,ART	–	PAS	HYST, ICUa(n), TOT, SRC,1MApgar,5MApgar
Huang et al. [91],2018, CN P	UAE, 11 C, 6	Previous CS,uterine surgeries	+	PAS	BL,RBC(U), TOT,HYST,ICUa(n), C-DgradeIV, ASless1,ASless5
Li et al. [69],2018, CN R	PBO.AO3, 33 PBO-IIA, 37 PBO,CIA, 42	Previous CS	+	PAS	BL, TOT, HYST,ICUa(n),1MApgar
Li et al. [70],2018, CN R	PBO-AO3, 24 C, 32	Previous CS,uterine surgeries	–	Placenta previa PAS	HYST,TOT,ICUa(n), AMSH,1MApgar,5MApgar,NICUa(n),NM
Mei et al. [71],2018, CN R	PBO-IIA, 20 C, 20	Previous CS	–	PAS	BL,RBC(U),TOT
Ono et al. [72],2018, CN R	PBO-CIA, 20 C, 20	NR	+	PAS	BL,TOT
Picel et al. [73],2018, CN R	PBO-IIA, 90 C, 61	Previous CS	+	Placenta previa PAS	BL,RBC(U),FFP(U),PLT(U)
Sun et al. [74],2018, CN R	PBO-AO3, 19 C, 12	Previous CS	+	Placenta previa PAS	BL,LOS,SRC,1MApgar,5MApgar
Cho et al. [75],2017, KOR R	PBO-IIA, 18 C, 59	Previous CS,ART	–	Placenta previa PAS	HYST,ICUa(n)

Table 1 (continued)

Author, year, country Study design	Intervention, n	Known risk factors	Confirmed PAS(IO or HP)	Type of abnormal placentation antepartum known	Outcomes
Cui et al. [76],2017, CN R	PBO-AO3, 38 C, 31	Previous CS	+	PAS	TOT,BL,RBC(U),FFP(U),PLT(U),Cryo(U), HYST, SRC, C-DgradeIV,ASless1, ASless5
Fan et al. [92],2017, CN P	PBO-IIA, 74 C, 89	Previous CS	–	PAS	BL,AMSH,HYST,TOT,5MApgar,NICUa(n)
Feng et al. [93],2017, CN P	PBO-IIA, 30 C, 11	NR	–	PAS	TOT,ICUa(n),BL,RBC(U), AMSH, ASless1
Pan et a l. [77],2017, CN R	UAE 26 C, 19	Previous CS,ART	+	PAS	HYST,ASless1, ASless5
Wang et al. [94],2017, CN P	PBO-AO3, 10 C, 33	Previous CS	+	Placenta previa PAS	HYST,BL,C-D gradeIV,NM
Xie et al. [95],2017, CN P	PBO-IIA, 30 C, 41	Previous CS	+	PAS	BL,TOT,HYST,SRC,NICUa(n)
Zeng et al. [78],2017, CN R	PBO-IIA, 48 C, 38	Previous CS,uterine surgeries	+	Placenta previa PAS	BL,RBC(U),FFP(U),Cryo(U),PLT(U), HYST,TOT,ICUa(n),AMSH,SRC,1MApgar,5MApgar,NICUa(n)
Al-Hadethi et al. [79],2016, AU R	PBO-CIA, 25 C, 27	NR	+	PAS	HYST,SRC
Wu et al. [80],2016, CN R	PBO-AO3, 230 C, 38	NR	+	Placenta previa PAS	HYST, TOT,BL,ICUa(n), C-DgradeIV,1MApgar,5MApgar
Chen et al. [81], 2016, CN R	PBO-AO3, 20 C, 23	Previous CS	–	Placenta previa	BL,TOT, C-DgradeIV,,HYST,AMSH,NM
Broekman et al. [82],2015, NL R	PBO-IIA, 42 C, 26	NR	+	Placenta previa	BL, TOT
Salim et al. [38],2015, ISRL RCT	PBO-IIA, 13 C, 14	Previous CS,uterine surgeries	–	PAS	RBC(U),FFP(U),PLT(U),Cryo(U), BL, HYST,SRC,TOT, ASless5,NM
Ballas et al. [83],2012, US R	UAE, 59 C, 58	Previous CS	+	PAS	BL, RBC(U),FFP(U),PLT(U),TOT,SRC,AMSH
Panici et al. [96],2012, ITA P	PBO-AO3, 15 C, 18	Previous CS,uterine surgeries,ART	+	Placenta previa PAS	HYST,,BL,RBC(U),ICUa(n)
Tan et al. [84],2012, CN R	PBO-IIA, 11 C, 14	Previous CS	+	PAS	BL, TOT

Abbreviation: *NR* indicates not reported, *BL* blood loss, *HYST* peripartum hysterectomy, *MassT* massive transfusion, *C-Dgrade IV* Clavien-Dindo grade IV post-operative complications, *SRC* surgical-related complications, *TOT* total operative time, *LOS* length of stay, *ICUa* intensive care unit admission, *RBC* red blood cells, *PLT* platelets, *FFP* fresh frozen plasma, *Cryop* cryoprecipitates, *MM* maternal mortality, *NA* neonatal asphyxia, *NICUa* neonatal intensive care admission, *NM* neonatal mortality, *ASless1* Apgar score less than 7 at 1 min, *ASless5* Apgar score less than 7 at 5 min.

classification bias, intervention bias, missing data bias, outcomes measurement bias, and reporting bias. The categories of judgment for each study were low, moderate, serious, and critical risk of bias. To guide interpretation of the confidence in the effect estimates, the certainty of the evidence was graded into four levels according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines [23]: high, moderate, low or very low.

Data synthesis

We performed an arm-based random effect frequentist network meta-analysis [24]. Raw data was extracted using 2 × 2 tables for each outcome measured. When data were reported as median and interquartile range, the mean and SD were estimated according to calculations per Luo et al. [25] and Wan et al. [26], respectively. For studies that reported data as median and range, a technique described by Hozo et al. [27] was used to calculate an estimate of the mean and SD.

For dichotomous variables, the risk ratio (RR) was chosen as the effect size. For continuous variables, the standardized mean difference (SMD) was chosen as the effect size. Generalized DerSimonian-Laird [28] estimator was used to estimate the between-study variance, assumed as common for each pairwise treatment comparison. A generalized I^2 was adopted to define heterogeneity as follows: low (< 25%), moderate (25–75%), or high (> 75%)

[29]. To account for transitivity, the eligibility criteria of the included studies are framed in such a manner that the trials are primarily different in the tested interventions only. To assess transitivity, we generated descriptive statistics and compare the distributions of baseline characteristics across studies and treatment comparisons [30]. It was not possible to conduct a formal assessment of the local inconsistency given network open loops. The treatment ranking probability was estimated with the cumulative ranking curve (SUCRA). The network geometry was appraised and the confidence of outcomes estimates was assessed with Confidence in Network Meta-Analysis (CINeMA) instrument. Two-sided *p*-values were considered statistically significant when less than 0.05, and the confidence intervals (CI) were computed at 95%. Where necessary we estimated standard deviation from range [31]. All analyses and graphs were carried out using R-CRAN statistical software with *netmeta* package [32]. Outliers was also performed.

Results

Study selection

The primary literature search yielded 3360 records, of which 2394 were unique. After reviewing titles and abstracts, we identified 70 articles that were eligible for full-text screening. Two studies were excluded because of missing data for the primary and secondary outcomes [33, 34], two studies reporting outcomes on women undergoing peripartum hysterectomy were also excluded, and one study was not included because did not quantitatively subgroup patients undergoing prophylactic placement of occlusive balloons [35]. Overall, 61 met eligibility criteria for qualitative and quantitative analysis. The flowchart of the study selection process is shown in Fig. 1.

Study characteristics

Table 1 outlines demographic, clinical and operative data of the included studies. Overall, 6973 women with suspected or confirmed abnormal placentation undergoing prophylactic endovascular procedures or not were included. Of those, 2996 (42.9%) did not undergo any endovascular procedure, 1865 (26.7%) underwent REBOA, 1162 (16.6%) PBO-IIA, 406 (5.8%) PBO-CIA placement, and 544 (7.8%) underwent UAE. Three RCTs [36–38] included 95 women undergoing prophylactic PBO-IIA, and 92 controls. Fifty-eight observational studies included a total population of 3885 patients undergoing prophylactic endovascular procedures and 2904 controls; among those, there were forty-four were retrospective cohort studies [39–84], and fourteen prospective cohort studies [85–96]. Most studies came from Asia [36–65, 67–78, 80, 81, 84–86, 88, 90–95], three from North America [66, 83, 87], three form Europe [82, 89, 96], and one from Australia [79]. The mean patient's age ranged from 27 to 39 years. Parity was outlined in eight studies and ranged from 1 to 7. History of caesarean section or uterine surgery (D&C, curettage,myomectomy) and ART use were specified each study. Abnormal placentation was confirmed intraoperatively or histopathological in 41 studies (67.2%). Bladder injury was the most widely reported surgery-related complication. Grade IV post-operative complications according to Clavien-Dindo classification system [32] occurred in up to 2, 4% of the patients.

Risk of bias of the included studies

Quality assessment of randomized and non-randomized studies is depicted in Supplemental Figs. 1 and 2, respectively. The overall quality of the evidence, according to the GRADE approach [45], was moderate to low for primary outcomes. (Supplemental Table 5).

Synthesis of results

Table 2 provide detailed results of pair-wise meta-analysis for primary and secondary outcomes (League Table).

The network plots for primary outcomes are shown in Fig. 2.

Forest plots of the network meta-analysis for primary outcomes are depicted in Fig. 3.

Heterogeneity of the global network was found in primary and secondary outcomes (Supplemental Tables 1 and 3). Funnel plot for publication bias was not assessed because of insufficient studies and therefore cannot be excluded.

Primary outcomes

Blood loss

Blood loss (estimated or quantitative) was reported in fifty observational studies [36–45, 47–62, 65–69, 71–74, 76, 78, 80–89, 91–96] and in three RCT [36–38] (5150 patients). The pooled network meta-analysis found that women with prophylactic endovascular interventions had on average a lower volume of perioperative blood loss compared to controls. The standardized mean differences were −1.80 L (95% CI −2.38; −1.21) for prophylactic REBOA, −0.15 L (95% CI −0.77;0.47) for prophylactic PBO-IIA, −1.36 L (95% CI −2.82;0.11) for prophylactic PBO-CIA, and −1.77 L (95% CI −2.97; −0.56) for prophylactic UAE. Blood loss was also significantly reduced for REBOA and UAE groups, compared to PBO-IIA group (SMD −1.65 L, 95% CI −2.45; −0.86 and SMD RR −1.62 L, 95% CI −2.97; −0.27). The same findings were confirmed in the subgroup analysis according to placental disorder, including 22 studies reporting on patients with PAS (Supplemental Table 2). However, heterogeneity

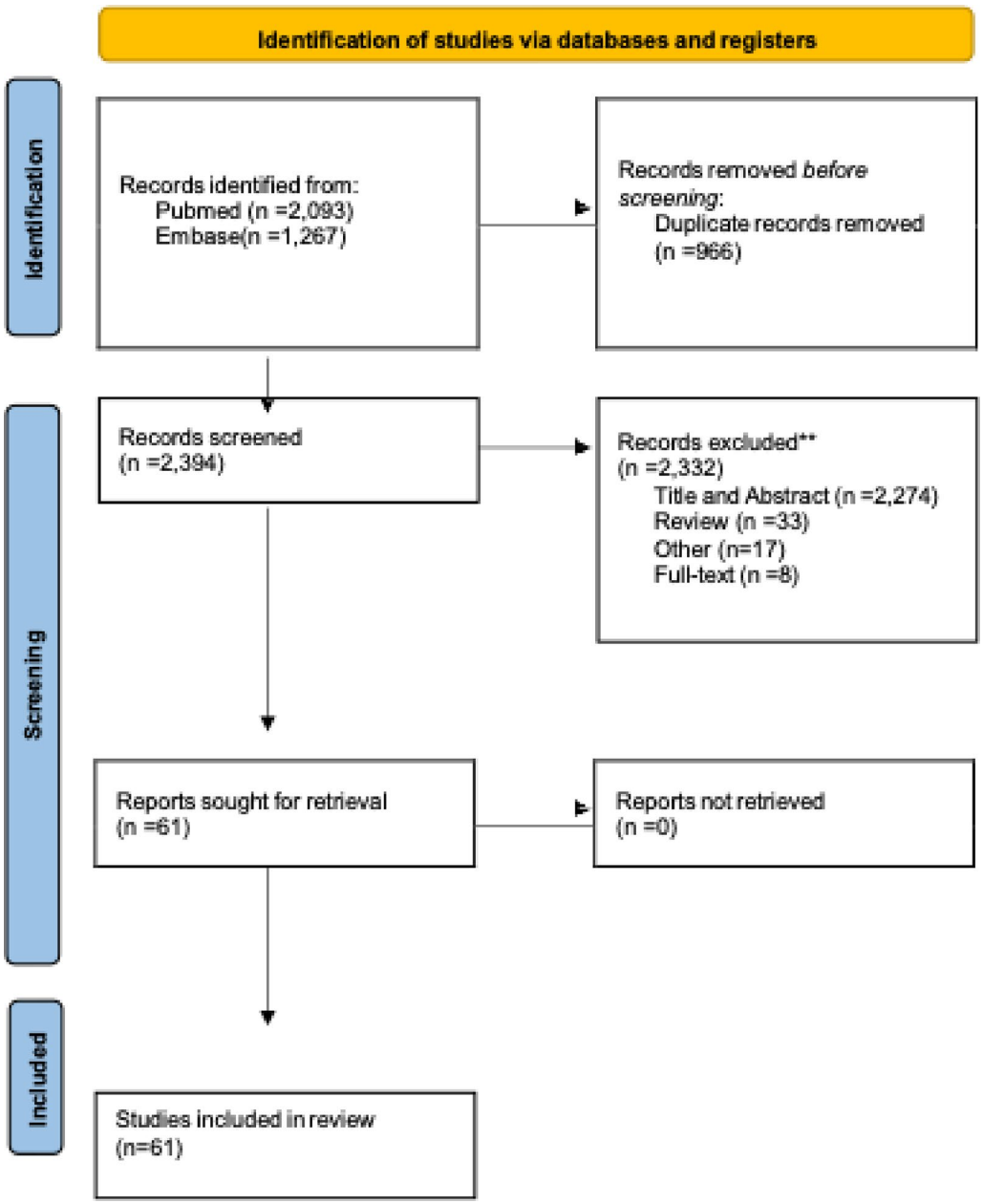

Fig. 1 PRISMA 2020 flow diagram

between studies was high (Supplemental Table 1 and 3). The subgroup analysis including 8 studies reporting on patients with placenta previa failed to find any significant difference among REBOA and PBO-IIA groups (Supplemental Table 2) contributing to a discrete reduction of heterogeneity (Supplemental Table 3; $I^2 = 89.4\%$).

Peripartum hysterectomy

Peripartum hysterectomy rate was reported in forty-three observational studies [36–40, 42–46, 49–60, 63–65, 67–70, 75–81, 85, 86, 88–92, 94–96] and in three RCTs [36–38] (4875 patients). The pooled network meta-analysis found that peripartum hysterectomy rates were significantly lower in the REBOA and UAE groups compared to controls (Table 2; RR 0.45, 95% CI 0.32;0.62 and RR 0.49, 95% CI 0.26;0.92). Peripartum hysterectomy rates were also significantly lower in the REBOA group compared to PBO-IIA group (Table 2; RR 0.47, 95% CI 0.30;0.73). Heterogeneity between studies was moderate-high (Supplemental Table 1; I^2: 66.2%). These findings

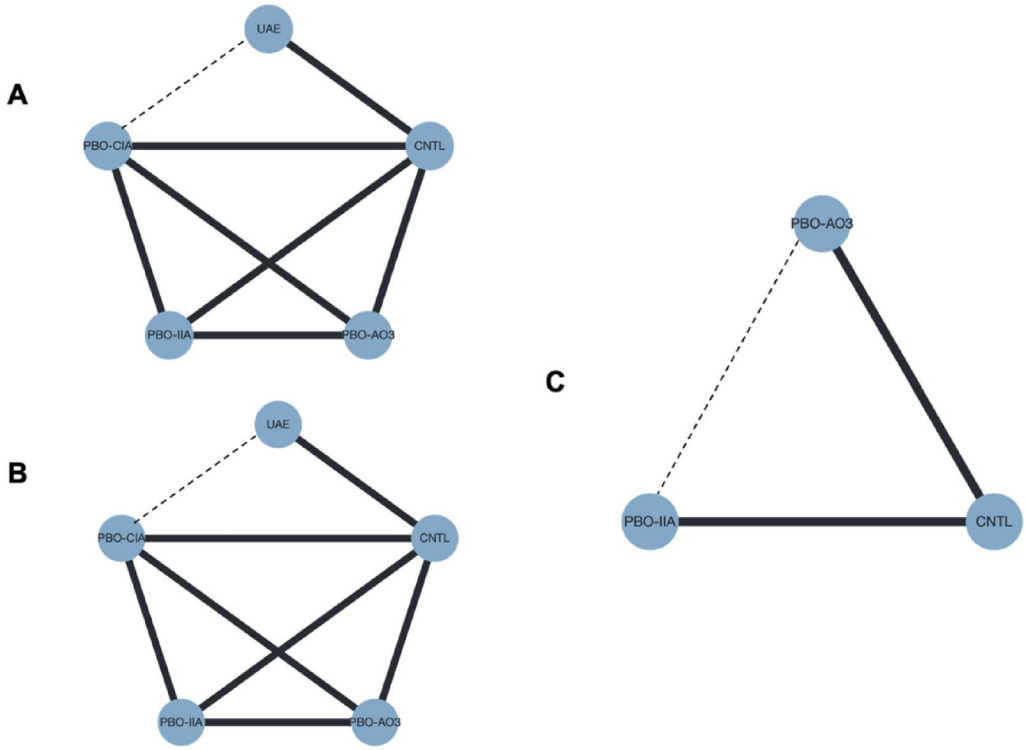

Fig. 2 Network geometry for studies reporting **A** blood loss; **B** peripartum hysterectomy and **C** massive transfusion

were confirmed in the subgroup analysis of patients with PAS in which peripartum hysterectomy rates were also significantly reduced in the UAE group compared to PBO-IIA (Supplemental Table 2; RR 0.44, 95% CI 0.24;0.81), contributing to a considerable reduction of heterogeneity (Supplemental Table 3; $I^2 = 4.4\%$). The subgroup analysis according to placental disorder found that only REBOA was associated with lower rates of peripartum hysterectomy compared to controls in patients with placenta previa, with an about fourfold risk ratio increase in controls as compared to the intervention group (Supplemental Table 2; RR 0.21, 95% CI 0.0.6;0.75) within a low-grade heterogeneity among the treatment groups (Supplemental Table 3; I2 = 20.6%).

Massive transfusion

Massive transfusion rate was reported in four observational studies [47, 52, 85, 87] (687 patients). The pooled network meta-analysis found that REBOA was associated with a significant decrease in massive transfusion rates compared to PBO-IIA and controls (Table 2; RR 0.37, 95% CI 0.20;0.70 and RR 0.47, 95% CI 0.27;0.80), within a global heterogeneity of zero (Supplemental Table 1; $I^2 = 0\%$). A subgroup analysis according to placental disorder was not possible due to lack of data.

Secondary outcomes

Maternal outcomes

The most widely described maternal outcomes were surgery-related complications (3,746 patients in three randomized [36–38] and 22 non-randomized trials [39, 42–44, 46, 47, 49, 51–54, 56, 57, 66, 74, 76, 78, 79, 83, 85–87, 90, 95]), total operative time (3,676 participants in three randomized [36–38] and 36 non-randomized trials [37, 41–45, 47, 48, 56–58, 60–62, 64, 68–72, 76, 78–86, 88–93, 95]), ICU admissions (2451participants in 2 randomized [36, 37] and 19 non-randomized trials [42, 44, 48, 52, 57, 64, 66, 69, 70, 75, 78, 80, 85, 87, 89–91, 93, 96]), units of RBC transfused (2333 patients in three randomized [36–38] and 21 non-randomized trials [42, 43, 47, 50, 51, 55, 58, 59, 67, 71, 73, 76, 78, 83, 85, 87, 91, 93, 96]), and Clavien-Dindo grade IV post-operative complications (2016 patients in one randomized [37] and 18 non-randomized trials [42–45, 47, 55, 56, 59, 65, 67, 76, 80, 81, 85, 86, 91, 94]), Other outcomes included units of platelets transfused (972 participants in two randomized [36, 38] and 7 non-randomized trials [50, 52, 73, 76, 78, 83, 85]), units of fresh frozen plasma transfused (940 participants in 2 randomized [36, 38] and 6 non-randomized trials [43, 52, 73, 76, 78, 83, 85]), units of cryoprecipitates transfused (477 participants in 2 randomized [36, 38] and 5 non-randomized trials [43, 47, 76, 78, 85]), maternal

Table 2 League table for primary and secondary outcomes

Maternal outcomes				
Blood loss				
CNTL	**1.80(1.21;2.38)**	1.36(−0.11;2.82)	0.15(−0.47;0.77)	**1.77(0.56;2.97)**
−1.80(−2.38;−1.21)	PBO-AO3	−0.44(−1.88;0.99)	**−1.65(−2.45;−0.86)**	−0.03(−1.37;1.30)
−1.36(−2.82;0.11)	0.44(−0.99;1.88)	PBO-CIA	−1.21(−2.75;0.33)	0.41(−1.48;2.31)
−0.15(−0.77;0.47)	**1.65(0.86;2.45)**	1.21(−0.33;2.75)	PBO-IIA	**1.62(0.27;2.97**)
−1.77(−2.97;−0.56)	−1.77(−2.97;−0.56)	−0.41(−2.31;1.48)	**−1.62(−2.97;−0.27)**	UAE
Peripartum hysterecomy				
CNTL	**2.32(1.68;3.21)**	1.44(0.60;3.47)	1.08(0.75:1.56)	**2.04(1.09;3.84)**
0.43(0.31;0.60)	PBO-AO3	0.62(0.25;1.55)	**0.47(0.30;0.73)**	0.88(0.43;1.79)
0.70(0.29;1.68)	1.61(0.65;4.03)	PBO-CIA	0.75(0.30;1.87)	1.42(0.48;4.20)
0.93(0.64;1.34)	**2.15(1.37;3.37)**	1.33(0.53;3.32)	PBO-IIA	1.89(0.91;3.92)
0.49(0.26;0.92)	1.13(0.56;2.30)	0.70(0.24;2.08)	0.53(0.25;1.09)	UAE
Massive transfusion				
CNTL	**2.14(1.25;3.65)**	0.79(0.57;1.10)		
0.47(0.27;0.80)	PBO-AO3	**0.37(0.20;0.70)**		
1.26(0.91;1.75)	**2.69(1.44;5.05)**	PBO-IIA		
Surgery-related complications				
CNTL	**1.52(1.09;2.13)**	0.31(0.01;7.25)	0.85(0.56;1.30)	0.69(0.41;1.14)
0.66(0.47;0.92)	PBO-AO3	0.20(0.01;4.85)	**0.56(0.33;0.96)**	**0.45(0.25;0.83)**
3.24(0.14;75.87)	4.93(0.21;117.58)	PBO-CIA	2.76(0.11;66.58)	2.23(0.09;54.32)
1.17(0.77;1.79)	**1.79(1.04;3.06)**	0.36(0.02;8.74)	PBO-IIA	0.81(0.42;1.56)
1.45(0.88;2.41)	**2.21(1.21;4.06)**	0.45(0.02;10.97)	1.24(0.64;2.40)	UAE
Total operative time				
CNTL	**0.76(0.15;1.36)**	0.43(−0.89;1.75)	−0.23(−0.88;0.42)	**−1.81(−3.24;−0.38**)
−0.76(−1.36;−0.15)	PBO-AO3	−0.32(−1.60;0.95)	**−0.99(−1.77;−0.21)**	**−2.57(−4.12;−1.02)**
−0.43(−1.75;0.89)	0.32(−0.95;1.60)	PBO-CIA	−0.66(−2.05;0.72)	**−2.25(−4.19;−0.30)**
0.23(−0.42;0.88)	0.99(0.21;1.77)	0.66(−0.72;2.05)	PBO-IIA	**−1.58(−3.15;−0.01)**
1.81(0.38;3.24)	**2.57(1.02;4.12)**	**2.25(0.30;4.19)**	**1.58(0.01;3.15)**	UAE
ICU admission				
CNTL	**1.92(1.29;2.85)**	2.01(0.56;7.20)	1.08(0.68;1.71)	1.67(0.43;6.48)
0.52(0.35;0.77)	PBO-AO3	1.05(0.29;3.76)	**0.56(0.32;0.98)**	0.87(0.21;3.57
0.50(0.14;1.78)	0.96(0.27;3.43)	PBO-CIA	0.54(0.16;1.86)	0.83(0.13;5.34)
0.92(0.59;1.46)	1.78(1.02;3.09)	1.86(0.54;6.45)	PBO-IIA	1.55(0.37;6.46)
0.60(0.15;2.32)	1.15(0.28;4.71)	1.20(0.19;7.73)	0.65(0.15;2.70)	UAE
Units of RBC transfused				
CNTL	**1.25(0.68;1.82)**	0.34(−0.17;0.85)	1.03(−0.01;2.08)	
−1.25(−1.82;−0.68)	PBO-AO3	**−0.91(−1.64;−0.18)**	−0.22(−1.41;0.97)	
−0.34(−0.85;0.17)	**0.91(0.18;1.64)**	PBO-IIA	0.69(−0.47;1.86)	
−1.03(−1.08;0.01)	0.22(−0.97;1.41)	−0.69(−1.86;0.47)	UAE	
Clavien-Dindo grade IV post-operative complications				
CNTL	**3.06(1.56;5.99)**	1.35(0.05;37.97)	1.20(0.44;3.29)	0.91(0.37;2.24)
0.33(0.17;0.64)	PBO-AO3	0.44(0.02;11.59)	0.39(0.12;1.32)	**0.30(0.10;0.91)**
0.74(0.03;20.94)	2.27(0.09;59.85)	PBO-CIA	0.89(0.03;29.23)	0.67(0.02;21.41)
0.83(0.30;2.27)	2.54(0.76;8.53)	1.12(0.03;36.59)	PBO-IIA	0.75(0.19;2.91)
1.10(0.45;2.72)	**3.37(1.09;10.41)**	1.48(0.05;47.21)	1.33(0.34;5.13)	UAE
Units of PLT transfused				
CNTL	0.42(0.06;0.78)	−0.01(−0.28;0.26)	−0.00(−0.52;0.52)	
−0.42(−0.78;−0.06)	PBO-AO3	−0.43(−0.88;0.02)	−0.42(−1.06;0.21)	
0.01(−0.26;0.28)	0.43(−0.02;0.88)	PBO-IIA	0.01(−0.58;0.59)	
0.00(−0.52;0.52)	0.42(−0.21;1.06)	−0.01(−0.59;0.58)	UAE	

Table 2 (continued)

Units of FFP transfused				
CNTL	0.88(0.01;1.76)	0.36(−0.15;0.86)	0.59(−0.50;1.68)	
−0.88(−1.76;−0.01)	PBO-AO3	−0.52(−1.53;0.49)	−0.29(−1.69;1.10)	
−0.36(−0.86;0.15)	0.52(−0.49;1.53)	PBO-IIA	0.23(−0.97;1.43)	
−0.59(−1.68;0.50)	0.29(−1.10;1.69)	−0.23(−1.43;0.97)	UAE	
Units of Cryoprecipitates transfused				
CNTL	0.43(−0.26;1.12)	−0.69(−1.51;0.13)		
−0.43(−1.12;0.26)	PBO-AO3	**−1.12(−2.19;−0.05)**		
0.69(−0.13;1.51)	**1.12(0.05;2.19)**	PBO-IIA		
Maternal mortality				
CNTL	0.80(0.09;7.55)	0.70(0.03;16.19)		
1.25(0.13;11.71)	PBO-IIA	0.87(0.02;41.33)		
1.43(0.06;33.15)	0.87(0.02;41.33)	UAE		
Uterine compression sutures				
CNTL	0.60(0.33;1.09)	0.86(0.62;1.18)	2.68(0.94;7.60)	
1.17(0.85;1.60)	PBO-AO3	1.43(0.73;2.81)	**4.47(1.34;14.84)**	
1.17(0.85;1.60)	0.70(0.36;1.37)	PBO-IIA	**3.13(1.05;9.30)**	
0.37(0.13;1.06)	**0.22(0.07;0.74)**	**0.32(0.11;0.95)**	UAE	
Bilateral uterine artery embolization				
CNTL	1.67(0.80;3.48)	1.22(0.51;2.90)		
0.60(0.29;1.25)	PBO-AO3	0.73(0.27;1.98)		
0.82(0.34;1.97)	1.37(0.50;3.73)	PBO-IIA		
Neonatal outcomes				
Apgar score at 1 min				
CNTL	0.02(−0.45;0.49)	0.01(−1.35;1.37)	0.26(−0.25;0.77)	0.36(−1.214;1.94)
−0.02(−0.49;0.45)	PBO-AO3	−0.02(−1.37;1.34)	0.24(−0.42;0.90)	0.34(−1.31;1.98)
−0.01(−1.37;1.35)	0.02(−1.34;1.37)	PBO-CIA	0.25(−1.10;1.60)	0.35(−1.73;2.43)
−0.26(−0.77;0.25)	−0.24(−0.90;0.42)	−0.25(−1.60;1.10)	PBO-IIA	0.10(−1.56;1.76)
−0.36(−1.946;1.21)	−0.34(−1.98;1.31)	−0.35(−2.43;1.73)	−0.10(−1.76;1.56)	UAE
Apgar score at 5 min				
CNTL	−0.01(−0.48;0.45)	0.47(−0.05;1.00)		
0.01(−0.45;0.48)	PBO-AO3	0.49(−0.17;1.15)		
−0.47(−1.00;0.05)	−0.49(−1.15;0.17)	PBO-IIA		
1 min Apgar score less than 7				
CNTL	0.96(0.35;2.63)	0.29(0.01;7.68)	1.06(0.26;4.38)	
1.04(0.38;2.83)	PBO-AO3	0.31(0.01;9.26)	1.10(0.19;6.24)	
3.39(0.13;88.47)	3.27(0.11;99.30)	PBO-IIA	3.59(0.10;125.81)	
0.95(0.23;3.91)	0.91(0.16;5.19)	0.28(0.01;9.76)	UAE	
5 min Apgar score less than 7				
CNTL	0.91(0.19;4.48)	1.11(0.10;12.04)	0.22(0.01;3.26)	
1.09(0.22;5.36)	PBO-AO3	1.21(0.07;21.28)	0.24(0.01;5.49)	
0.90(0.08;9.83)	0.83(0.05;14.54)	PBO-IIA	0.20(0.01;7.25)	
4.61(0.31;69.37)	4.22(0.18;97.68)	5.10(0.14;189.00)	UAE	
NICU admission				
CNTL	0.98(0.49;1.95)	0.88(0.76;1.01)		
1.14(0.99;1.31)	PBO-AO3	1.12(0.56;2.25)		
0.73(0.54;1.00)	0.72(0.34;1.52)	PBO-IIA		
Neonatal asphyxia				
CNTL	0.91(0.19;4.48)	1.11(0.10;12.04)	0.22(0.01;3.26)	
1.09(0.22;5.36)	PBO-AO3	1.21(0.07;21.28)	0.24(0.01;5.49)	
0.90(0.08;9.83)	0.83(0.05;14.54)	PBO-IIA	0.20(0.01;7.25)	

Table 2 (continued)

4.61(0.31;69.37)	4.22(0.18;97.68)	5.10(0.14;189.00)	UAE
Neonatal mortality			
CNTL	2.57(0.45;14.57)	0.96(0.10;9.02)	
0.39(0.07;2.24)	PBO-AO3	0.37(0.07;6.42)	
1.04(0.11;9.81)	2.68(0.16;45.94)	PBO-IIA	

Bold values indicate $p < 0.05$

Values are expressed as Risk Ratio (RR) or Weighted mean differences (WMD) and 95% Confidence Intervals (95% CI)

NICU indicates neonatal intensive care

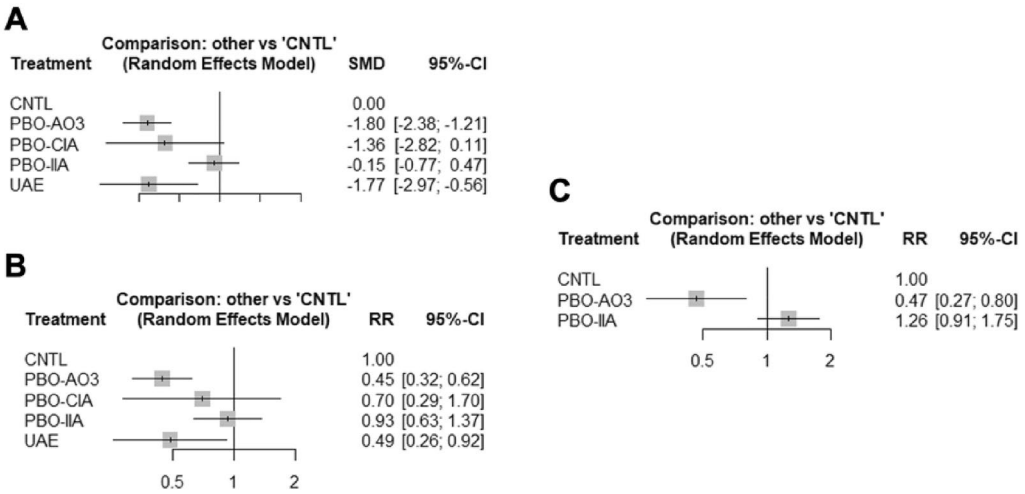

Fig. 3 Forest plots of the network meta-analysis estimates the risk ratio (RR) for primary outcomes (**A** blood loss; **B** peripartum hysterectomy and **C** massive transfusion)

mortality (207 participants in one randomized [36] and 3 non-randomized trials [43, 53, 54, 63]), and the use of additional haemostatic procedures such as, uterine compression sutures (644 participants in 1 randomized [36] and 6 non-randomized trials [47, 53, 88, 89, 92, 93]), and post-operative bilateral uterine artery embolization (1,344 participants in one randomized [36] and 12 non-randomized trials [43, 44, 50, 51, 55, 61, 68, 78, 88, 92]).

The pooled network analysis showed that surgery-related complications were significantly reduced for REBOA compared to PBO-IIA (RR 0.56, 95% CI 0.33;0.96), UAE (RR 0.45, 95% CI 0.25;0.83) and controls (RR 0.66, 95% CI 0.47;0.92), within a global heterogeneity of zero($I^2 = 0\%$). The subgroup analysis according to placental disorder in patients with PAS revealed that surgery-related complications were significantly reduced for REBOA compared only to controls (RR 0.45, 95% CI 0.26;0.78, $I^2 = 0\%$). Surgery-related complications of patients with placenta previa were insufficiently reported; therefore, they were not analysed.

Total operative time was also significantly reduced for REBOA compared to PBO-IIA (SMD −0.99 min, 95% CI −1.77; −0.21), UAE (SMD −2,57 min, 95% CI −4.12; −1.02) and controls (SMD −0.76 min, 95% CI −1.36; −0.15). The pooled network analysis and the subgroup analysis according to placental disorder of patients with PAS showed that total operative time was significantly increased in the UAE group compared to REBOA (RR 6.09 min, 95% CI 4.11;8.07), PBO-IIA (RR 5.18 min, 95% CI 3.19;7.17), PBO-CIA (RR 5.85 min, 95% CI 3.61;8.09), and controls (RR 5.77 min, 95% CI 3.92;7.61). However, heterogeneity between studies was high (Supplemental Tables 1 and 3). Data regarding total operative time of patients with placenta previa were insufficiently reported; therefore, they were not analysed.

ICU admissions and units of RBC transfused were significantly reduced in the REBOA group compared to PBO-IIA (RR 0.56, 95% CI 0.32;0.98 and SMD −0.91, 95% CI −1.64; −0.18) and controls (RR 0.52, 95% CI 0.35;0.77 and SMD −1.25, 95% CI −1.82; −0.68);within a global heterogeneity of 40.3% (Supplemental Table 1). However, the subgroup analysis according to placental disorder of patients with PAS showed that ICU admissions were significantly reduced in the REBOA group compared only to controls (Supplemental Table 2; RR 0.48, 95% CI 0.26;0.91); whereas no significant differences were found

for units of RBC transfused among the treatment groups in patients with PAS (Supplemental Table 2), contributing to a considerable reduction of heterogeneity (Supplemental Table 3; $I^2=0\%$). Data on ICU admissions and units of RBC transfused of patients with placenta previa were insufficiently reported; therefore, they were not analysed.

Clavien-Dindo grade IV post-operative complications were significantly higher in the UAE group (RR 3.37, 95% CI 1.09; 10.41) and controls (RR 3.06, 95% CI 1.56;5.99) compared to REBOA, within a low grade of heterogeneity ($I^2=26.3\%$) among studies; while the subgroup analysis according to placental disorder of patients with PAS showed that Clavien-Dindo grade IV post-operative complications were significantly reduced in the REBOA group compare only to controls (RR 0.45, 95% CI 0.26;0.78) within a global heterogeneity of zero ($I^2=0\%$). Clavien-Dindo grade IV post-operative complications of patients with placenta previa were insufficiently reported; therefore, they were not analysed.

Units of FFP transfused were significantly reduced in the REBOA group compared to controls (Table 2; SMD −0.42, 95% CI −0.78; −0.06 and SMD −0.88, 95% CI −1.76; −0.01) whereas units of cryoprecipitates transfused were significantly reduced in REBOA group compared to PBO-IIA (Table 2; SMD −1.12, 95% CI −2.19; −0.05); the heterogeneity among studies was high (Supplemental Table 11). The subgroup analysis according to placental disorder of patients with PAS did not find any significant difference among the treatment groups regarding units of cryoprecipitates transfused (Supplemental Table 2). Data on units of FFP and cryoprecipitates transfused of patients with placenta previa were insufficiently reported; therefore, they were not analysed.

Lastly, UAE was associated with a lower rate of uterine compression sutures compared to women undergoing prophylactic placement of REBOA (RR 0.22, 95% 0.07;0.74) and PBO-IIA (RR 0.32, 95% CI 0.11;0.95). Subgroup analysis according to the type of abnormal placentation was not possible due to lack of data.

No significant differences were found for units of platelets transfused, maternal mortality and use of post-operative bilateral uterine artery embolization among the treatment groups.

Neonatal outcomes

The most widely described neonatal outcomes were 1 min Apgar score (2555 patients in 21 non-randomized trials [39, 40, 42–44, 49–52, 54, 55, 57, 66, 69, 70, 74, 78, 80, 85, 86, 88, 90],) and 5 min Apgar score (2148 patients in 18 non-randomized trials [39, 42–44, 49–51, 54, 55, 57, 58, 66, 70, 74, 78, 80, 86, 88, 90, 92],). Other outcomes included NICU admission (1617 patients in one randomized [36] and 8 non-randomized trials [42, 47, 52, 70, 78, 88, 92, 95]), 1 min Apgar score less than 7 (640 patients in 7 non-randomized trials [47, 49, 60, 76, 77, 91, 93],), 5 min Apgar score less than 7 (942 patients in 2 randomized [36, 38] and 5 non-randomized trials [47, 49, 76, 77, 91]), neonatal asphyxia (1617 patients in 5 non-randomized trials [44, 47, 52, 63, 68]), and neonatal mortality (647 patients in one randomized [38] and 4 non-randomized trials [43, 70, 81, 94]). No significant differences were found for 1 and 5 min Apgar scores, 1 and 5 Apgar scores less than 7, neonatal intensive care unit admissions, neonatal asphyxia, and neonatal mortality among the treatment groups.

No evidence was available to determine the effect of different prophylactic endovascular procedures on long-term outcomes, such as fertility and reproductive outcomes, quality of life and costs. No outliers were detected.

Endovascular procedures-related complications

Adverse events related to the prophylactic endovascular intervention were reported in two randomized trials [36, 38] and 52 non-randomized trials [36–38, 40–45, 47, 51–53, 55, 57, 58, 60–62, 64–89, 91–96] (Supplemental Table 4). Overall, complication rates related to endovascular procedures in patients undergoing prophylactic endovascular procedures were 1.61% (n = 17/1055) for PBO-IIA, 5.52% for REBOA (n = 73/1278), 5.86% for PBO-CIA (n = 17/290), and 1.01% for UAE (n = 3/116).

Complication rates requiring only clinical observation was 68.4%(50/73) for patients undergoing prophylactic placement of REBOA, 41.1%(7/17) for PBO-IIA, 82.3%(14/17) for PBO-CIA, and 66.6%(2/3) for UAE. Complication rates requiring any conservative or surgical intervention were 31.5%(23/73) for REBOA, 58.8%(10/17) for PBO-IIA, 17.6%(3/17) for PBO-CIA, and 33.3%(1/3) for UAE. Irreversible complications such as uterine atrophy and necrosis was reported in one case of UAE.

The main complication requiring conservative or surgical intervention in the REBOA group was non-occlusive femoral artery (FA) thrombosis, which occurred in 26% (n = 19/73) of patients. Of these, 15 patients (79%) recovered with conservative therapy and 4 required surgical thrombectomy (21%). Forty-six patients (63%) experienced weakened or non-palpable pulsation of the dorsalis pedis artery which recovered spontaneously before discharge. No balloon ruptures, displacement or ischemic events occurred in the REBOA group. Five patients (0.5%) in the PBO-IIA group experienced arterial thrombosis (2 in the external iliac artery, 1 non-occlusive and 1 occlusive in the FA, and 1 in the popliteal artery) and other five patients (0.5%) had femoral access

wound hematoma which recovered spontaneously before discharge. A balloon rupture and catheter displacement occurred in two patients, and two patients had leg pain and weakness without swelling and ischemia and buttock claudication and abdominal pain, respectively. Complications occurred in the PBO-CIA group were: 13 patients experienced weakened or non-palpable pulsation of the dorsalis pedis artery which recovered spontaneously before discharge, 2 patients had traumatic dissection of the common iliac artery causing thromboembolic events that required surgical thrombectomy. Catheter displacement was reported in PBO-CIA group without specifiyng the exact number of patients. One patient undergoing prophylactic UAE had uterine atrophy and necrosis and another patient experienced occlusive FA thrombosis which required surgical thrombectomy. Lastly only a few studies reported on the use or not of an anticoagulant prophylaxis, as measure to prevent thromboembolic events in these patients.

Discussion

Principal findings

This is the first comprehensive study reporting pooled data and multiple outcomes on patients with any type of abnormal placentation, including placenta previa. Our results suggests that prophylactic endovascular procedures before a planned cesarean section in women with abnormal placentation are associated with reduced perioperative blood loss. This effect was more pronounced among women undergoing prophylactic UAE and REBOA. Similarly, peripartum hysterectomy rates were significantly lower in women undergoing prophylactic UAE and REBOA compared to the control group. REBOA was also associated with a significant decrease in massive transfusion rates, surgery-related complications, ICU admissions, and units of RBC tranfused, compared to PBO-IIA and control groups. Moreover, women not undergoing prophylactic endovascular procedures and women undergoing prophylactic UAE showed a significant increase in total operative time and Clavien-Dindo grade IV post-operative complications compared to REBOA.

Subgroup analysis according to placental disorder revealed that patients with placenta previa without prophylactic placement of any endovascular procedure had a a 4 to fivefold increased risk of peripartum hysterectomy compared to women undergoing prophylactic placement of REBOA. Conversely, peripartum hysterectomy rates and ICU admissions were significantly reduced in the UAE group compared to PBO-IIA and in the REBOA group compared to controls in patients with PAS, respectively. All prophylactic endovascular procedures had a comparable risk ratio in terms of units of platelets transfused, maternal mortality, and use of additional post-operative bilateral uterine artery embolization among the treatment groups. As for neonatal outcomes, no significant differences were detected.

Comparison with existing literature

Although systematic review and meta-analysis have reported encouraging results on the use of prophylactic endovascular procedures in reducing peripartum blood loss and the associated morbidity in patients with PAS [10, 11], subsequent studies showed inconsistent results on their effectiveness and safety. Moreover, this meta-analysis is the first to include pooled data of patients with placenta previa.

Our main analysis, in line with previous quantitative analysis, reveals differences in outcomes among the four interventions, with proximal balloon occlusion (REBOA) having the strongest effect [13–19]. It is speculated that, given the extensive collateral blood supply to the uterus, embolization or balloon occlusion at distal sites may not be as effective as occlusion at the abdominal aorta Zone 3 (infrarenal).Thus, in addition to reducing morbi-mortality associated with catastrophic hemorrhage, proximal balloon occlusion may also allow for fertility preservation, by reducing peripartum hysterectomy rates, especially in women with placenta previa according to our findings. UAE is an effective minimally invasive treatment for PPH, however its prophylactic use remains controversial because of long term fertility concerns and the irreversible effects on the uterus [97, 98].

REBOA, originally used in the US Military Army for trauma surgery [99] has now evolved with multiple applications in the civilian trauma and obstetric population [100]. This minimally invasive procedure may have some distinct advantages such as easier and faster catheterization, bedside placement using only external landmarks (without use of radiation or fluoroscopy), with a high level of reported technical success and safety [87, 101, 102]. The experience from trauma surgery has indeed demonstrated that multidisciplinary collaboration between gynaecologists and surgeons can improve their clinical comfort with the placement of REBOA [103]. Efforts to strengthen surgical systems and global surgery has led to the development of national surgical, obstetrics and anaesthesia plans (NSOAPs) which has been recognized as powerful strategies to accelerate the achievement of the United Nations Sustainable Development Goals for achieving health, welfare, and economic development by 2030 [104, 105].

However, studies included in this network meta-analysis did not specify standard location of occlusion within zone 3 of the aorta (3A vs. 3B), except one [87], and this distinction may be important because of the risk of ischemic complications and the extensive collateralization of pelvic vessels in the late pregnancy. Notably, only two studies [87, 106] have investigated prophylactic placement of REBOA for pelvic bleeding control in the distal portion of aortic Zone 3 (between the inferior mesenteric artery and the aortic bifurcation, at the level of the third lumbar vertebra; Zone 3B). These studies concluded that more distal occlusion preserves the benefits of proximal Zone 3 aortic occlusion while reducing the risk of colonic and ovarian ischemia, potentially allowing for longer occlusion time (up to 60 min). The use of aortic occlusive procedures has indeed raised concern due to the potential severe associated complications, especially arterial thrombosis, pseudoaneurysm, and ischemic events, occasionally requiring additional interventions. A consistent variability and lack in reporting adverse events across studies was noted in our series, thus definitive interpretations cannot be made and further studies taking extensively these variables into account are needed.

More recently, use of smaller access sheaths to mitigate REBOA complications has been advocated; these are specifically designed to have even safe overinflation ability and enable more control on deflation for partial-REBOA applications [107, 108]. The low profile is specifically important in reducing access site complications in pregnant female patients who are often hypercoagulable and have smaller blood vessels. The COBRA-OS 4- French catheter aims to decrease patient's discomfort, reduce the risk of bleeding complications and is specifically designed to be fluoroscopy-free, eliminating the need for tracking over a wire [108].

Lastly, in line with previous reports, no significant effect on neonatal outcomes were reported within the prophylactic UAE or placement of endovascular occlusive balloons.

Strengths and limitations

Compared with previously published meta-analyses [10–12], this network meta-analysis, compared all the available evidence regarding different prophylactic endovascular procedures, including patients with placenta previa for the first time. Our subgroup analysis according to the type of placental disorder, when data was available, showed stable results for almost all the primary and secondary outcomes, contributing, in some cases, to a considerable reduction of the heterogeneity. However, we must acknowledge some limitations in this study. First, it is based on both RCTs and observational studies, with consequent risks of confounders like heterogeneity and sample size. Also, the predominance of observational studies in the analysis warrants caution in the interpretation of the results of this meta-analysis. Owing to the lack of randomized trials, further clinical trials with larger populations and stratification based on the type of placental disorder (placenta previa versus accreta) will be needed in the future to determine whether there are more significant differences between the approaches than have thus far been revealed. The high level of heterogeneity for some outcomes maybe explained by the fact that PAS disorder is characterized by a wide range of severities, from accreta to the most severe form, placenta percreta. Thus, the overall estimated effect to different severities of PAS disorder should not be generalized. Moreover, using blood loss as a primary outcome has some recognized limitations, as there is inherent inaccuracy in estimating the volume of postpartum blood loss as variation in the methodology of estimation across studies [109].

Regarding the overall applicability of the evidence, there was a substantial variation in inclusion criteria between studies, which made difficult to extrapolate recommendations for everyday practice. This meta-analysis included forty-one studies (67.2%) reporting on women with a confirmed placental disorder diagnosis, intraoperatively or histopathologically, and this distinction may be crucial because the decision to opt for a prophylactic endovascular procedure is always made antepartum, leading to a potential overtreatment.

Studies on prophylactic embolization had sever or critical risk of bias together with wide CI as a result of the small sample size, limiting our ability to interpret the results of this intervention. Finally, the assessments of confidence in the estimates using CINeMA showed low confidence, essentially due to study limitation, imprecision, and inconsistence. When interpreting treatment rankings, caution is advised due to the lack of consideration for the magnitude of differences between treatments, potentially explained by chance.

Conclusions and implications

Preventing PPH or temporizing patients until definitive haemorrhage control can be achieved remains a high priority in the obstetric setting worldwide. Prophylactic endovascular interventional procedures, particularly aortic balloon occlusion, may improve clinical outcomes in women with abnormal placentation. Given the potential procedure-related complications, critically identifying

patients who may benefit from prophylactic endovascular procedure is warranted. Optimal management of these patients requires multidisciplinary collaboration with well-designed algorithms and institutional protocols for the antepartum and postpartum management. The recent emergence of new endovascular balloon devices specifically designed to decrease the possible procedure-related complications may increase safety while improving outcomes.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13017-025-00602-w.

Supplementary material 1.

Supplementary material 2. Fig. 1. Risk of bias according to ROB-II tool.

Supplementary material 3. Fig. 2. Risk of bias according to ROBINS-I tool.

Supplementary material 4.

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Author contributions
GBNV: designed the study protocol, performed the literature search, contributed to interpretation of the results and wrote the initial manuscript draft and revisions; ABLF: designed the study protocol design, supervised analyses and contributed to interpretation of the results, drafted the manuscript and revisions; GBNT: contributed to study design, performed and supervised the statistical analyses and performed critical revision; AA: performed the statistical analysis and contributed to the study protocol design; NS: performed the statistical analysis and contributed to the study protocol design; MC: contributed to the design of this study protocol, revised the drafts and provided critical revision and PIC: contributed to the study protocol design, supervised analyses and contributed to interpretation of the results, drafted the manuscript and revisions. All the authors participated in discussions on the study design and results and approved the final version to be published. All authors have agreed to be held accountable for all aspects of this study.

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Competing interests
The authors declare no competing interests.

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