Role of interventional radiology in pregnancies complicated by placenta accreta spectrum disorders: a systematic review and meta-analysis

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Abstract

Objective: To determine the potential benefit of the interventional radiology (IR) in improving the outcome of women undergoing surgery for placenta accreta spectrum (PAS) disorders.

Methods: Medline, Embase and CINAHL databases were explored searching a robust cadre of terms relating to PAS. The primary outcome was the intraoperative estimated blood loss (EBL,L); Secondary outcomes were: units of packed red blood cells (PRBC) fresh frozen plasma (FFP), platelets (PLT) cryoprecipitate transfused, operative time (min), length of hospital stay (d), EBL ≥2.5 L, PRBC transfused ≥5 units, surgical complications, bladder ureteral injuries, re-laparotomy, infection, disseminated intravascular coagulation (DIC) and complications related to endovascular catheter placement. Only studies reporting the incidence of or the mean difference in the observed outcomes in women affected by PAS disorders who had compared to those who did not have IR procedures before surgery were considered for the inclusion. All these outcomes were explored in the overall population of women with a prenatal diagnosis of PAS and in those undergoing hysterectomy. Quality assessment of each included study was performed using the Risk of Bias In Non-randomized Studies–of Interventions tool (ROBINS-I). The GRADE methodology was used to assess the quality of the body of retrieved evidence.

Results: Fifteen studies (955 women) were included. Mean EBL ((MD -1.01, 95% CI-1.59; -0.43); p<0.001) and the risk of EBL ≥2.5 L (OR 0.18, 95% CI 0.04-0.78, p=0.02) were significantly less in the cases compared to controls. There was no significant difference in the other outcomes explored. In the subgroup analysis of pregnancies complicated by PAS undergoing hysterectomy, the EBL (MD -0.68; 95% CI -1.24, -0.12, p=0.02) and the number of transfused FFP units (MD -1.66; 95% CI -2.71, -0.61, p=0.02) were significantly less in women undergoing endovascular IR procedures compared to controls. Furthermore, women undergoing IR had a significantly lower risk of requiring transfusion of ≥5 PRBC units (OR 0.10, 95% CI 0.02-0.47, p=0.04). Overall, the complications related to the placement of endovascular catheter occurred in 5.3% (95% CI 2.6-8.9; I2 65.3%) of the pregnancies undergoing IR. Overall quality of evidence, as qualified by GRADE, was low.

Conclusion: The current data available provide encouraging evidence that IR procedures may be associated with lower EBL and rates of transfusion in pregnancies complicated by PAS disorders**.** However, given the overall very low quality of the evidence, as reflected in the GRADE assessment, further large studies are needed in order to confirm the beneficial role of IR in improving the outcome of women undergoing surgery for PAS disorders.

Introduction

Rise in caesarean section rate over the last two decades has led to a massive increase in the incidence of placenta accreta spectrum (PAS) disorders[1-3].

Prenatal diagnosis of PAS disorders, either by ultrasound or magnetic resonance imaging (MRI), has been shown to improve the maternal outcome by allowing a pre-planned treatment of these anomalies, while the presence of a multidisciplinary team involving expert surgeons and anesthesiologists and the prompt availability of blood products are fundamental in order to reduce the risk of acute intraoperative complications[4,6].

Despite this, the optimal surgical approach to PAS disorders is still to be determined and there is no randomized controlled trial comparing the different management options.

Cesarean hysterectomy is currently the definitive treatment method for PAS disorders, although recently described conservative techniques aiming at removing the part of the uterus invaded by the placenta, such as one step conservative surgery and Triple-P procedure, have been shown to represent a reasonable option to hysterectomy, although they have not been evaluated in randomized trials[4,6].

Endovascular interventional radiology (IR) procedures are commonly used in the management of post-partum hemorrhage (PPH) of various causes.[7] These techniques involve bilateral placement of embolization and/or balloon catheters (BC) through the femoral arteries under fluoroscopic guidance and have been suggested to reduce the amount of blood loss, improve visualization of the operative field and reduce surgical complications[2]. A recent health care commission investigating maternal deaths in the United Kingdom acknowledged the potential role of IR in reducing maternal mortality and the Royal College of Obstetricians and Gynecologists (RCOG) recommended the early involvement of interventional radiology in the management of PPH and instigation of protocols to include interventional radiology either in response to PPH or in women at high risk of PPH[8].

Yet, there are conflicting results on the role of such procedures in improving the surgical outcome of women affected by PAS disorders in the recently published literature.

Small sample size, retrospective design, lack of a control group and the large heterogeneity in gestational age at delivery, type of surgical treatment, endovascular techniques explored and severity of placental invasion among the previously published studies are likely to account for such discrepancies and do not allow the extrapolation of a robust evidence on the actual role of IR procedures in improving the outcome of pregnant women undergoing surgery for PAS disorders.

The main aim of this systematic review was to determine the potential benefit of the IR in improving the outcome of women undergoing surgery for PAS disorders. A secondary aim was to quantify the risk of the procedure-related complications in these pregnancies.

Methods

Data sources

This review was performed according to an a-priori designed protocol and recommended for systematic reviews and meta-analysis[9-10]. MEDLINE, Embase and CINAHL were searched electronically on the 21st December 2017 utilizing combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for "abnormal invasive placenta" "morbidly adherent placenta", and "outcome" (Supporting information 1). The search and selection criteria were restricted to English language. The reference lists of relevant articles and reviews were hand searched for additional reports. The Prisma guidelines were followed[11]. This study was registered with the PROSPERO database (Registration number: CRD42018083834).

Eligibility criteria, main outcomes and measures

Inclusion criteria were studies including women with a prenatal diagnosis of PAS undergoing compared to those not undergoing IR procedure.

The primary outcome was the mean difference of the intraoperative estimated blood loss (EBL) (L) in women who had compared to those who did not have IR procedures before surgery.

Secondary outcomes were:

- Number of transfused Red blood cells (PRBC) (units)
- Number of transfused Fresh frozen plasma (FFP) (units)
- Number of transfused Platelets (PLT) (units)
- Number of transfused Cryoprecipitate (units)
- Operative time (minutes)
- Length of hospital stay (days)
- EBL ≥2.5 Liter (L)
- Transfused packed red blood cells (PRBC) ≥5 units
- Surgical complications, including damage to adjacent organs such the bowel, bladder and ureters.
- Bladder or ureteral injuries
- Re-laparotomy
- Surgical site infection, defined as any infection occurring within 30 days of operation related to the operation itself or the postoperative course, including superficial incisional, deep incisional, organ or space infection and sepsis[12].
- Disseminated intravascular coagulation (DIC).

- Complications related to endovascular catheter placement, including bleeding, hematoma, thrombosis, limb ischemia, dissection or perforation of the vessels, peripheral artery injury, fasciotomy, infection or balloon rupture.

All these outcomes were first explored in the overall population of women who had a prenatal diagnosis of PAS, irrespective of the type of surgical approach adopted. Furthermore, we investigated the same outcomes in women with a prenatal diagnosis of PAS disorders undergoing hysterectomy, in order to reduce the potential source of bias given by pooling together cases undergoing different surgical strategies. Finally, we stratified the analysis according to the type of IR procedure adopted to report the incidence of complications related to BC placement.

Only studies reporting the incidence of or the mean difference in the observed outcomes in women with a prenatal diagnosis of PAS who had compared to those who did not have IR procedures before surgery were considered eligible for the inclusion in the systematic review. Studies not reporting a control group, those without a clear confirmation of PAS disorders, those from which cases diagnosed prenatally could not be extrapolated and those reporting the use of IR procedures exclusively in acute conditions, such as cases presenting with massive hemorrhage in the setting of undiagnosed PAS disorders, were excluded. Finally, studies published before 2000 were excluded, as we considered that improvements in the diagnosis and management of PAS disorders make these less relevant.

Prospective and retrospective case-control studies, case reports and case series were analyzed. Opinions, cases series with less than three cases per group and case reports were also excluded in order to avoid publication bias.

Study selection and data collection

Two reviewers (FDA, AI) independently extracted data. Inconsistencies were discussed among the reviewers and consensus reached. For those articles in which the relevant information was not reported but the methodology was such that the information might have been recorded initially, the authors were contacted requesting the data. Histopathological findings and/or surgical findings were used as the gold standard for the diagnosis of PAS disorders. On histopathology, PAS disorders were defined according to the presence and degree of trophoblastic invasion through the myometrium and assessed on histopathological analysis of the removed uterus. Placenta accreta was diagnosed when anchoring placental villi were attached to myometrium rather than decidua, but without completely invading it; placenta increta when chorionic villi penetrated the myometrium, while the diagnosis of placenta percreta was considered when chorionic villi penetrated through the

myometrium to the uterine serosa and/or adjacent organs. Conversely, on surgery, PAS was diagnosed when there was a lack of spontaneous complete separation of the placenta from its basal plate requiring manual removal or after direct visualization placental tissue protruding through the uterine serosa[2].

Quality assessment of each included study was performed using the Risk Of Bias In Non-randomized Studies–of Interventions tool (ROBINS-I)[13]. ROBINS-I provides a detailed framework for assessment and judgement of risk of bias that may arise due to confounding, selection of participants into the study, measurement of interventions, departures from intended interventions, missing data, measurement of outcomes, and selection of reported results[13]. The ROBINS-I tool is equally appropriate for cross-sectional and longitudinal non-randomized studies as quality assessments are independent of study design. Each domain is determined to exhibit low, moderate, serious, or critical risk of bias. Low risk indicates that the study is "comparable to a well-performed randomized trial" in the domain being evaluated. Moderate risk of bias indicates the study is "sound for a non-randomized study" but not comparable to a rigorous randomized trial. Serious risk of bias indicates the presence of "important problems," while critical risk of bias indicates the study is "too problematic" to provide any useful evidence on the effects of intervention". If insufficient information is provided to determine the risk of bias of a certain domain, the domain is marked as having no information. All studies were analyzed using this tool regardless of whether the original study design included randomization to other exposures, thus ensuring that risk of bias was assessed specifically for the comparisons of interest to this review[13]. The GRADE methodology was used to assess the quality of the body of retrieved evidence (GRADEpro, Version 20. McMaster University, 2014)[14].

Statistical analysis

We used random-effect head-to-head meta-analyses, expressing the results as summary odds ratios (OR) with their 95% Confidence Interval (CI) for categorical variables or mean differences (MD) (with their 95% CI) for continuous outcomes. When single study results were reported as median and ranges, we used the method described by Hozo et al [13] to obtain the corresponding means and standard deviations (SD), and when the interquartile ranges (IQR) rather than ranges were reported, they were divided by 1.35 to obtain the equivalent SD. In all meta-analyses, the statistical heterogeneity was quantified using the I^2 metric.

Finally, we performed meta-analyses of proportions to estimate the pooled incidence of each categorical outcome in women who underwent pre-delivery trans-catheter arterial balloon occlusion compared to those who did not, either considering all women together and performing separate

analyses for each of the above-mentioned subgroups. Proportion meta-analyses were performed using a random-effect model to account for the inter-study heterogeneity and were not performed when only one study could be included.

Publication bias was explored graphically, through funnel plots, and formally, through Egger's regression asymmetry test. Formal tests for funnel plot asymmetry were not performed when the total number of publications included for each outcome was <10 as in this case the power is too low to distinguish chance from real asymmetry[16]. RevMan 5.3 (The Cochrane Collaboration, 2014) and Stata, version 13.1 (Stata Corp., College Station, TX, 2013) were used to analyze the data.

Results

General characteristics

A total of 971 articles were identified. After screening the abstracts, 291 full text articles were assessed with respect to their eligibility for inclusion (Supplementary Table 1) and 15 studies were included in the systematic review (Table 1, Figure 1, Supplementary Table 2)[18-32]. The 15 studies included 955 women undergoing surgery for PAS disorders; out of these 575 underwent IR while 380 did not have any endovascular procedure performed at the time of surgery and were considered as the control group.

When considering the depth of the placental invasion, 64.3% (95% CI 59.6-68.7) of women in the IR group and 70.0% (95% CI 63.1-76.1) of those not undergoing such procedures had placenta accreta or increta at histopathological analysis, while the corresponding figures for placenta percreta were 35.7% (95% CI 31.3-40.4) and 30.0% (95% CI 23.9-36.9).

Details of the risk of bias assessments for each study are reported in Table 2. One study was at generally low risk, eleven at moderate and three at critical risk of bias. There was only one randomized controlled trial comparing IR vs no endovascular procedure in women undergoing surgery for PAS disorders, while the other studies were retrospective case control series. However, in the large majority of such retrospective series, pregnancy characteristics, gestational age at surgery and type of surgical procedure performed were balanced between cases and controls, thus reducing the overall risk of bias on the reported results. The small number of cases in some of the included studies, dissimilarity of the populations and lack of stratification according to the severity of PAS, type of surgical approach adopted and gestational age at surgery represent their major weaknesses. Testing for publication bias could be performed only for 2 out meta-analyses and revealed no increased risk of bias (Supplementary material).

Synthesis of the results

Thirteen studies (821 women) explored the difference in EBL between the pregnancies which had IR procedure before surgery compared to those which did not. The mean EBL (MD -1.01, 95% CI -1.59; -0.43); $p<0.001$) and the risk of EBL ≥2.5 L (OR 0.18, 95% CI 0.04-0.78, p=0.02) were significantly less in the cases compared to controls (Table 3, Figure 2). There was no significant difference in the other outcomes explored (Tables 3 and 4). In a subgroup analysis of the pregnancies with a prenatal diagnosis of PAS disorders undergoing hysterectomy, the EBL (MD -0.68; 95% CI -1.24, -0.12, p=0.02) and the number of transfused FFP units (MD -1.66; 95% CI -2.71, -0.61, p=0.02) were significantly less in women undergoing endovascular IR procedures

compared to controls. Furthermore, women undergoing IR had a significantly lower risk of requiring transfusion of ≥units of PRBC (OR 0.10, 95% CI 0.02-0.47, p=0.04) (Table 4). Proportion meta-analysis: pooled rates of each categorical outcome in women with a diagnosis of PAS disorders treated compared to those not treated with IR are shown in Supplementary Table 3.
A comprehensive data synthesis on the type of IR technique and site of BC placement was possible only for internal iliac artery (IIA) and infra-renal aorta (IRA) catheterization. Women undergoing IIA and IRA catheterization had lower EBL (MD -0.40, 95% CI -0.62, -0.17 and -1.79; 95% CI -2.90. -0.67, respectively) compared to controls, although the analysis was affected by the very small number of cases included which might have potentially biased the results and which precluded to perform a comprehensive comparison between the two techniques (Supplementary Table 4 and 5).

Finally, we reported the incidence of procedure-related complications in women undergoing endovascular IR procedures. Overall, the complications related to the placement of endovascular catheter occurred in 5.3% (95% CI 2.6-8.9; I2 65.3%) of the pregnancies undergoing IR. When stratifying the analysis according to the site of catheter placement, complications occurred in 3.7% (95% CI 1.8-6.4, I^2 21.3%) of women having BC in the IIA and in 1.7% (95% CI 0.7-3.3. I^2 0%) of those undergoing aortic catheterization. A detailed description of the type of procedure-related complications is provided in the Supplementary Table 6.

GRADE

Overall evidence was qualified using GRADE pro. Overall, very low quality of evidence shows that endovascular IR are effective in reducing blood loss in women undergoing surgery for PAS disorders. The level of evidence for RCTs was downgraded due to considerable clinical and statistical heterogeneity (Supplementary Table 7).

Discussion

Main findings

The findings from this systematic review showed that endovascular IR procedures before surgery in women affected by PAS disorders are associated with a reduced amount of blood loss and need for transfusion, which persist when considering cases treated with hysterectomy. The small number of included cases did not allow a meaningful comparison between the different techniques. Finally, the risk of procedure-related complications ranged between 2 and 5%. Overall quality of evidence, as qualified by GRADE, was low. This means that further research is very likely to have an important impact on our confidence in estimating the role of IR in affecting the outcome of women undergoing surgery for PAS disorders and is likely to change the estimate.

Strengths and limitations

The small number of cases in some of the included studies, their retrospective non-randomized design, dissimilarity of the populations (due to various inclusion criteria) and lack of stratification of the results according to the depth of placental invasion, gestational age at birth, type of endovascular procedure performed, time at balloon insufflation and site of catheter placement represent the major limitations of this systematic review. Inclusion of mainly non-randomized studies represent the major limitation of the present systematic review. The key difference between randomized and non-randomized studies is the likelihood of groups being balanced on prognostic factors. Randomized trials are at generally low risk of selection bias because an adequate balance as regard as the most relevant prognostic factors is guaranteed RCTs by concealed randomization. Conversely, non-randomized trials are unlikely to be balanced. In this scenario, it might be entirely possible that some of the results reported in the present systematic review might have been affected by several co-factors not balanced between pregnancies undergoing and those not undergoing endovascular IR procedures, such as the gestational age at surgery, severity of PAS disorders and type of surgical approach. Furthermore, most of the included studies did not take into account the role of surgical expertise in managing these disorders. All these limitations downgrade the quality of evidence from this systematic review. In view of all these limitations, the quality of evidence of the present review was downgraded for each outcome based on other GRADE considerations (ie, study limitations, consistency of effect, imprecision, indirectness). Despite this, the present study remains the most comprehensive up to date on the role of IR techniques in women affected by PAS spectrum disorders

Implications for clinical practice

Despite its increasing prevalence, the optimal management of PAS disorders is yet to be defined.[1-4] The findings from this review provide encouraging evidence that IR procedures may be associated with lower EBL and rates of transfusion in pregnancies complicated by PAS disorders.

However, implementation of IR requires an accurate prenatal diagnosis of PAS disorders, because arrangement of such procedure may be difficult in acute conditions such as in women with undiagnosed PAS disorders.

Ultrasound is usually the primary imaging tool to screen woman at risk for PAS while MRI should be performed to confirm diagnosis and delineate the topography of invasion which cannot be always assessed on ultrasound. However, PAS can occur in a considerable proportion of women without classical risk factors, such as placenta previa and prior CS, thus questioning which sub-set of women should undergo detailed prenatal assessment to rule out the presence of morbidly adherent placenta[33]. Multiparametric prediction models integrating maternal, pregnancy and imaging characteristics have been shown to improve our ability to detect PAS disorders prenatally[34]. Furthemore, prenatal diagnosis of PAS disorders still requires standardization and it is affected by a high variability in the diagnostic performance among different centers[35,36].

Surgical management of PAS disorders represent another clinical challenge. There is no randomized controlled trial comparing the different management options in women affected by PAS disorders. Hysterectomy is currently the most common surgical approach performed in case of AIP although recent evidences suggest that more conservative techniques aiming at removing the area invaded by the placenta and restoring uterine and bladder anatomy may be as effective and safe as hysterectomy, although they require further validation.[4]

Endovascular IR techniques performed before surgery have been extensively used to treat post-partum hemorrhage of various causes, and recently claimed to improve the outcome of women undergoing surgery for PAS disorders. These procedures involve prophylactic preoperative placement of balloon catheters in several arteries supplying the uterus for occlusion and embolization after cord clamping in order to decrease blood loss and improve visualization of the operative field. IR has become an integral part of the multidisciplinary approach of women affected by PAS disorders, although the published literature reports contrasting results on their usefulness in clinical practice. Furthermore, the incidence of procedure-related complications has been reported as high as 15%. Small sample size of most of these studies, retrospective design, inclusion of

women undergoing emergency procedures and lack of stratification according to the type of surgical approach performed is likely to account for such differences.

The findings from this systematic review showed a beneficial effect of preoperative endovascular IR procedures in reducing blood loss and need for transfusion. This benefit persists when considering only women undergoing hysterectomy or those affected by placenta percreta. Furthermore, the incidence of the procedure-related complications was low.

Therefore, we support the use of preoperative balloon placement in women at high risk of AIP, although it is the collective authors' experience that there is a large variation in the hemostatic response to acute severe hemorrhage during surgery, even among the pregnancies with the same histopathological diagnosis of PAS disorders. These differences may be explained by the fact that PAS is not a unique condition but encompasses a wide range of disorders which may largely differ as regard to the depth, extension and location of placental invasion, which cannot be completely categorizes by a histopathological analysis.

Unfortunately, interventional radiologists skilled in post-partum hemostatic control are not available in every hospital facility, thus highlighting the need for a prompt referral of cases suspected to be affected by PAS to centers with high expertise not only in surgical management but also in IR techniques to control haemostaiss in women witrh PAS. Furthermore, despite all its limitation, this systematic review highlight the need

Conclusion

In pregnancies complicated by PAS**,** endovascular IR procedures were associated with lower EBL and need for transfuion, compared to the those who did not. Overall quality of evidence, as qualified by GRADE, was very low. Further large studies are needed in order to confirm the beneficial role of IR in improving the outcome of women undergoing surgery for PAS disorders, and to explore the optimal type of endovascular technique in terms of hemostasis control and complication rate.

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Figure legend

Figure 1. Systematic review flowchart.

Figure 2. Pooled mean difference in estimated blood loss between women receiving vs those not receiving interventional radiology procedures before surgery for PAS disorders.

Table 1. General characteristics of the studies included in the systematic review.

Author	Year	Country	Study design	Period considered	Reference standard	Outcomes explored	Surgical approach to PAS	PAS (n)	Site of catheter placement
Cui[18]	2017	China	Retrospective	2015-2016	Surgery, pathology	OT, EBL, PPRBC, FFP, PLT transfused, LOS, surgical complications	Hysterectomy, conservative surgery	69	AO
Fan[19]	2017	China	Prospective	2015-2017	Surgery	EBL, PPRBC transfused, OT, surgical complications	Hysterectomy, conservative surgery	163	IIA
Feng[20]	2017	China	Retrospective	2012-2014	Surgery	EBL, PPRBC, FFP, PLT transfused, OT, LOS	Hysterectomy, conservative surgery	41	IIA
Zeng[21]	2017	China	Retrospective	2014-2017	Pathology, surgery	EBL, BP transfused, OT, LOS, relaparotomy, surgical complications	Hysterectomy	104	AO
Wu[22]	2016	China	Retrospective	2012-2015	Surgery	EBL, OT, BP transfused	Hysterectomy, conservative surgery	268	AO
Pan[23]	2016	China	Retrospective	2012-2015	Surgery	EBL, PPRBC transfused	Conservative surgery, hysterectomy	45	UA
Salim[24]	2015	Israel	Randomized controlled trial	2009-2015	Surgery, pathology	PRBC transfused, EBL, OT, surgical complications, LOS	Hysterectomy, conservative surgery	24	IIA
Omar[25]	2015	United States	Retrospective	2003-2014	Surgery, pathology	EBL, PPRBC transfused requirements, OT, LOS	Hysterectomy, conservative surgery	42	CIA, IIA, UA
Cali[26]	2014	Italy	Prospective	2004-2013	Pathology, surgery	EBL, BP transfused, OT, LOS, surgical complications,	Hysterectomy	53	IIA
Chantraine[27]	2012	Belgium	Retrospective	2005-2011	Surgery and Pathology	Need for transfusion, infection	Hysterectomy, conservative surgery	8	UA
Panici[28]	2012	Italy	Prospective	2005-2011	Pathology, surgery	EBL, PPRBC transfused, LOS, DIC	Hysterectomy, conservative surgery	33	AO
Angstmann[29]	2010	Australia	Retrospective/prospective	2001-2009	Pathology	EBL, PPRBC transfused, need for transfusion, LOS, OT	Hysterectomy, conservative surgery	20	CIA
Shrivastava[30]	2007	United States	Retrospective	1995-2006	Pathology, surgery	EBL, OT, LOS, infection	Hysterectomy	50	IIA
Tan[31]	2007	Singapore	Retrospective	2001-2005	Clinical	EBL, PPRBC transfused	Hysterectomy, conservative surgery	25	IIA
Bodner[32]	2006	United States	Retrospective	2000-2002	Pathology, surgery	EBL, PPRBC transfused, OT, LOS, surgical complications	Hysterectomy	10	IIA

AO: abdominal aorta; CIA: common iliac artery; IIA: internal iliac arteries; UA: uterine arteries;

Table 2. ROBINS-I risk of bias assessment

Author	Confounding	Selection	Measurements of Intervention	Missing data	Measurements of outcomes	Reported results	Overall
Cui[18]	**Low**	**Critical**	**Low**	**Low**	**Moderate**	**Low**	**Moderate**
Fan[19]	**Low**	**Critical**	**Low**	**Low**	**Moderate**	**Low**	**Moderate**
Feng[20]	**Low**	**Critical**	**Low**	**Low**	**Moderate**	**Low**	**Moderate**
Zeng[21]	**Critical**	**Critical**	**Critical**	**Moderate**	**Moderate**	**Moderate**	**Critical**
Wu[22]	**Low**	**Critical**	**Moderate**	**Moderate**	**Moderate**	**Moderate**	**Moderate**
Pan[23]	**Low**	**Critical**	**Low**	**Low**	**Moderate**	**Low**	**Moderate**
Salim[24]	**Low**	**Critical**	**Low**	**Low**	**Moderate**	**Low**	**Low**
Omar[25]	**Low**	**Critical**	**Low**	**Low**	**Moderate**	**Low**	**Moderate**
Calì[26]	**Low**	**Critical**	**Low**	**Low**	**Moderate**	**Low**	**Moderate**
Chantraine[27]	**Critical**	**Critical**	**Critical**	**Moderate**	**Moderate**	**Moderate**	**Critical**
Panici[28]	**Moderate**	**Critical**	**Serious**	**Low**	**Moderate**	**Moderate**	**Moderate**
Angstmann[29]	**Low**	**Critical**	**Low**	**Low**	**Moderate**	**Low**	**Moderate**
Shrivastava[30]	**Low**	**Critical**	**Moderate**	**Moderate**	**Moderate**	**Moderate**	**Moderate**
Tan[31]	**Low**	**Critical**	**Low**	**Low**	**Moderate**	**Low**	**Moderate**
Bodner[32]	**Critical**	**Critical**	**Critical**	**Moderate**	**Moderate**	**Low**	**Critical**

Low risk of bias: The study is comparable to a well performed randomized trial with regard to this domain[13]
Moderate risk of bias: The study is sound for a non-randomized study with regard to this domain but cannot be considered comparable to a well performed randomized trial[13]
Serious risk of bias: The study has some important problems in this domain[13]
Critical risk of bias: The study is too problematic in this domain to provide any useful evidence on the effects of intervention[13]
No information (?): No information on which to base a judgement about risk of bias for this domain[13]

Table 3. Results of the head-to-head meta-analyses comparing selected continuous outcomes in women with a diagnosis of PAS disorders treated vs those not treated with IR. All outcomes were compared considering: all women with a prenatal diagnosis of PAS disorders; only women undergoing hysterectomy; only women with placenta percreta.

	N. studies (sample)	n/N*	Mean difference (95% CI)	p	I^2, %
All women					
- Blood loss (L)	13 (821)	493 / 328	-1.01 (-1.59; -0.43)	<0.001	98
- PRBC transfused (units)	9 (254)	131 / 123	-2.20 (-5.52; 1.13)	0.2	89
- FFP transfused (units)	3 (106)	56 / 50	-2.59 (-7.09; 1.92)	0.3	81
- PLT transfused (units)	4 (126)	64 / 62	-0.07 (-0.70; 0.55)	0.8	54
- Cryoprecipitate transfused (units)	4 (126)	64 / 62	-1.51 (-3.71; 0.68)	0.1	68
- Operative time (minutes)	11 (758)	470 / 288	-8.98 (-20.3; 2.38)	0.12	90
- Length of hospital stay (days)	11 (682)	448 / 234	-0.49 (-1.27; 0.29)	0.2	80
Women undergoing hysterectomy					
- Blood loss (L)	6 (258)	126 / 132	-0.68 (-1.24; -0.12)	0.02	83
- PRBC transfused (units)	5 (160)	79 / 81	-2.92 (-9.34; 3.50)	0.4	90
- FFP transfused (units)	3 (205)	105 / 100	-1.66 (-2.71; -0.61)	0.02	42
- PLT transfused (units)	3 (146)	72 / 74	-0.47 (-1.56; 0.62)	0.4	52
- Cryoprecipitate transfused (units)	2 (29)	13 / 16	-9.75 (-24.9; 5.39)	0.2	65
- Operative time (minutes)	5 (239)	118 / 121	9.72 (-12.7; 32.1)	0.4	67
- Length of hospital stay (days)	5 (248)	121 / 127	0.11 (-1.18; 1.40)	0.9	86

PRBC = Red blood cells. FFP = Fresh frozen plasma. PLT = Platelets. IIA = Internal iliac arteries. CI = Confidence Interval. n = Number of AIP women treated with interventional radiology; N = Number of AIP women not treated with interventional radiology.
*: Number of women complicated by PAS disorders treated (n) and not treated (N) with IR.

Table 4. Results of the head-to-head meta-analyses comparing the risk of each categorical outcome in women with a diagnosis of PAS disorders treated vs those not treated with IR. All outcomes were compared considering: all women with a prenatal diagnosis of PAS; only women undergoing hysterectomy; only women with a diagnosis of placenta percreta.

	N. studies (sample)	**Raw data * (n/N vs n/N)**	**Pooled OR (95% CI)**	**p**	**I^2,%**
All women with prenatal diagnosis of PAS					
- Blood loss ≥2.5L	5 (112)	17/58 vs 35/54	0.18 (0.04-0.78)	0.02	54
- PRBC transfused ≥5 Units	7 (158)	30/91 vs 37/67	0.45 (0.17-1.24)	0.12	33
- Surgical complications	9 (376)	29/198 vs 24/178	1.05 (0.58-1.90)	0.9	0
- Bladder-ureteral injures	7 (222)	15/115 vs 11/107	1.20 (0.52-2.79)	0.7	0
- Re-laparotomy	7 (226)	5/119 vs 7/107	0.82 (0.24-2.77)	0.8	0
- Infection	4 (65)	5/31 vs 4/34	1.26 80.31-5.12)	0.8	0
- DIC	4 (132)	4/67 vs 5/65	0.69 (0.17-2.91)	0.6	0
Women undergoing hysterectomy					
- Blood loss ≥2.5L	4 (155)	18/77 vs 49/78	0.10 (0.02-0.47)	0.004	40
- PRBC transfused ≥5 Units	4 (150)	24/74 vs 41/76	0.57(0.07-4.67)	0.6	62
- Surgical complications	6 (277)	30/126 vs 23/151	1.56 (0.84-2.87)	0.2	0
- Bladder-ureteral injures	5 (160)	13/67 vs 9/93	1.75 (0.69-4.43)	0.2	0
- Re-laparotomy	4 (152)	6/63 vs 8/89	1.47 (0.49-4.45)	0.5	0
- Infection	3 (97)	3/32 vs 4/65	1.49 (0.34-6.53)	0.6	0
- DIC	2 (78)	7/24 vs 12/54	1.25 (0.41-3.82)	0.7	0
- DIC	2 (72)	5/21 vs 11/51	0.66 (0.05-9.07)	0.8	42

***** The first "n/N" refers to e.g. the number of women complicated by PAS disorders treated with IR with a blood loss ≥2.5L (n) / the total number women complicated by PAS disorders treated with IR (N); the second "n/N" refers to e.g. the number of women complicated by PAS disorders not treated with IR with a blood loss ≥2.5L (n) / the total number women complicated by PAS disorders not treated with IR.