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HYSTERECTOMY VS PARTIAL MYOMETRIAL RESECTION FOR PLACENTA ACCRETA SPECTRUM (PAS). A FEASIBILITY STUDY OF A RANDOMIZED CONTROLLED CLINICAL EXPERIMENT (RCT-PAS)

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SEPTEMBER 2021

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1. SYNOPSIS

Data category	Information
Registration - Study ID Number	Clinical Trial.gov assigned number NCT05013749
Registration Date	August 18, 2021
Principal Sponsor	Centro de Investigaciones Clínicas – Fundación Valle del Lili. Cali, Colombia
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Public title:	RCT-PAS
Scientific Title:	Hysterectomy vs partial myometrial resection for placenta accreta spectrum (PAS). A feasibility study of a randomized controlled clinical experiment (RCT-PAS)
Recruitment coordination center:	Fundación Valle del Lili. Cali, Colombia
Recruitment centers:	3
Health Condition or Problem	Placenta Accreta Spectrum (PAS)
Study Type	Feasibility study of an open-label (non-blinded), randomized, controlled, multicenter clinical trial.
Primary objective	To evaluate the feasibility of the parallel experimental design, willingness of eligible patients to participate, and outcome measures for conducting a randomized phase III clinical trial comparing partial myometrial resection with hysterectomy in patients with PAD, conducted at 3 different centers, including the Fundación Valle del Lili, over a 24-month period.
Specific objectives	- Measure the proportion of eligible patients who agree to participate in this comparison. - To measure the percentage of screening failure. - Describe the confirmation of the presence or absence of placental accreta spectrum in each case. - To identify the degree of variability between the different methods of measuring intraoperative bleeding in each of the techniques.

Secondary objective	Clinical and sociodemographic characterization of the patient. To identify the characteristics of the patient's current pregnancy. To describe the clinical outcomes of interest in patients randomized to hysterectomy or partial myometrial resection. To categorize the severity of surgical complications according to the Clavien Dindo classification.
Study design	Feasibility study of randomized, controlled, multicenter clinical experiment on the use of partial myometrial resection vs. hysterectomy.
Intervention group	Patients with a confirmed diagnosis of PAD (See Appendix 2, Definition of a confirmed case of PAD) Partial myometrial resection.
Control	Patients with a confirmed diagnosis of PAD (See Annex 2, Definition of a confirmed case of PAD). Hysterectomy.
Population	Pregnant women with a prenatal ultrasound or MRI diagnosis of PAD (See Appendix 2: Definition of suspected case of PAD), who will be taken to surgery to treat this disease.
Inclusion Criteria	- Pregnant woman older than 18 years. - History of previous cesarean section and previous placenta previa. - Prenatal diagnosis by ultrasound or MRI of PAS (See Appendix 2: Definition of suspected case of PAS), regardless of the suspected degree of severity of the disease. - Requirement of surgical management of placental accreta on a scheduled basis. - Patients without active vaginal bleeding in the period immediately prior to surgery (Patients admitted to the operating room without active bleeding).
Exclusion Criteria	Women without previous living children.
Sample Size	60 participants
Randomization method	Permuted blocks of 4 and 6, stratified by center
Primary outcomes:	- Proportion of eligible patients who agree to participate in the study. - Percentage of screening failure. - Percentage of patients assigned to each arm of the study. - Percentage of patients with cross over between assigned arms of the study. - Number of subjects completing follow-up at 42 days postpartum.

Secondary outcomes:	- Maternal death - Intraoperative bleeding volume measured in mL. - Blood component transfusion requirement, median transfusion of red blood cell units (RBCs), platelets, fresh frozen plasma, cryoprecipitate and fibrinogen. - Compliance with at least one WHO Near Miss criterion (See Appendix 1). - Ureteral lesions. - Bladder lesions - Need for surgical reintervention. - Days of hospital stay in Intensive Care Unit. - Days of general and postoperative hospital stay. - Use of uterine tamponade with hydrostatic balloons. - Presence of supra fascial hematoma. - Presence of postoperative ileus. - Vital status of the newborn. - Weight of the newborn.
Statistical analysis	It will be performed according to the principles of intention-to-treat analysis. Descriptive statistics will be used to summarize the feasibility results. According to the CONSORT guidelines for feasibility experiments, efficacy tests are not recommended, because the study is not designed to detect differences between types of surgery, therefore, for clinical outcomes the analyses will focus mainly on descriptive analyses using mean (standard deviation) or median (interquartile range) for continuous outcomes and absolute frequencies and percentages for categorical outcomes. For the specific objective of the degree of variability of the bleeding methods, the coefficient of variation of each method within the surgical techniques will be calculated. The STATA software version 14.0 ® will be used.
Key Words	Placenta accreta spectrum, Hysterectomy, resective reconstructive treatment.

Amendment	1.0
Rationale	
Table of Contents	Included
Synopsis	Included
6.3 Specific objectives	Objective 1 is deleted: To evaluate the willingness of the team of gynecologists to recruit patients for a clinical experiment. This is eliminated because it would be 100% because the team of intensivist gynecologists of the placental accreta spectrum clinic have signed the log of responsibilities. Compliance with this agreement is difficult to measure because women who might be eligible are not known and were not identified by gynecologists. Objective 4 is deleted: To measure the frequency and describe the cross-over ratios in each group using random assignment of the intervention. This is eliminated because there is only one cross-over ratio. This ratio is described in section 9.4 Study groups of the protocol. Objective 5 is modified: The purpose of this objective is clarified, which is to measure how concordant the methods for measuring bleeding are. The secondary clinical outcomes or complications are by clinical diagnosis and there is no doubt about them. Objective 6 is deleted: To identify the administrative barriers to the performance of the randomly assigned procedure is eliminated because in this study there are no administrative withdrawals. Objective 7 is deleted: To evaluate the comparability and generalizability of the sample of patients studied is eliminated because in this type of study the patients are highly selected, with very strict criteria. Therefore, the comparability and generalizability is very low. The objective is added to describe the confirmation of the presence or absence of placental accreta spectrum in each case.
6.4 Secundary objectives	The objective is included: To categorize the severity of surgical complications according to the Clavien Dindo classification.
8.2 Secondary outcome measures	New secondary outcomes that were not contemplated in the previous version of the protocol are included.
9.6 Sample size	The sample size is specified according to the estimated recruitment rate for each center, the proposal is: 36 patients for Indonesia, 12 patients for Argentina and 12 patients for Colombia.
9.15 Interim analysis plan	The interim analysis plan is modified, it is proposed to perform this analysis when 10 patients have been randomized, proportional to the

	expected recruitment rate: 60% for the largest recruiter and 40% between the other two institutions.
9.10 Procedures flow chart	Included.
10. 1. Data collection	The affiliation of the Biomedical Research Ethics Committee is clarified: the Ethics Committee (IRB) belongs to the Fundación Valle del Lili and is independent of the Clinical Research Center.
10.3 Data quality monitoring	-The research team is appointed as an independent clinical monitor according to Good Clinical Practice guidelines. -Data verification times are adjusted to the recruitment rate. -Monitoring plan is defined.
11.2 Informed Consent	Typing error corrected, this protocol does not contemplate Legal Representation for the participants.
12.6 Safety and Adverse Event Evaluation Committee	Statistician independent of the research group is appointed according to Good Clinical Practice guidelines.
Appendix 3	Possible participant identification is deleted, box for eligibility confirmation is increased..
Appendix 4	Redesigned format for screening and randomization registry.
Appendix 5	The functions of the clinical coordinator of the study are adjusted, the figure of the sub-investigator is added.
Appendix 6	Redesigned format, added evaluation of the intensity of the event by the principal investigator
Appendix 9	Telephone contact form is designed for a follow-up visit at 42 days postpartum.

Amendment	2.0
6.3 Specific objectives	The objective is added to describe the confirmation of the presence or absence of placental accreta spectrum in each case.
6.4 Secundary objectives	The objective is included: To obtain a photographic and filmic record of the PAS prenatal diagnostic ultrasound, surgery and histopathology of all included cases, in order to verify the presence or absence of PAS in each patient.
9.7.1 Recruitment strategy: Selection	A paragraph of the recruitment strategy is modified to clarify the collection of photos and videos of prenatal ultrasound, surgery and histology of each case.
9.10 Procedures flow chart	The order of the follow-up visits provided for in the procedures flowchart is modified.

9.14 Statistical analysis plan	The statistical analysis plan is modified, including the coefficient of variation of the methods for measuring intraoperative bleeding.
9.15 Interim analysis plan	The specification of performing the analysis proportional to the expected recruitment rate is eliminated.
10. 1. Data collection	It is specified that information about the result of the histopathological study of the surgical specimen will be collected.
10.2.3 Medical visit between 7 and 12 days	The option of follow-up between 7 and 12 days through telemedicine has been added.
15. Variables tables	The following variables are added: confirmation of PAS by histopathology, degree of invasion of PAS according to histopathology. The numbering of the response options for the dichotomous variables was corrected, it was clarified that admission to the ICU is related to PAS, and the wording of some variables was corrected.
16. White tables	The pertinent corrections are made in white tables taking into account the corrections made in the variable tables. Table 5 represents the coefficient of variation of the methods for measuring intraoperative bleeding, is added.
Appendix 4	The screening and enrollment format of the study is modified, the name of the institution is added as the title of the table, the date of screening, age and assignment group are added for each patient according to inclusion and exclusion criteria.
Appendix 5	The role is added to the principal investigator and co-investigator of taking photos during the surgical procedure. The option of follow-up between 7 and 12 days through telemedicine has been added. The deadlines for recording variables in Red Cap® have been modified to a suggested period of 48 hours and maximum 7 days.

	The name of the Clinical Coordinator of the study is modified, Dr. Lina María Vergara retires and Dr. Stiven Sinisterra Díaz joins the team. The description of the procedure for disclosure of randomization by the clinical coordinator is modified. Added role for the study coordinator to provide support to the PI in the collection of PAS prenatal diagnostic ultrasound photos and histology. The functions of the clinical coordinator of the study are adjusted, the figure of the sub-investigator is added.
Appendix 10: Standardized surgical technique manual and photographs	A detailed step-by-step description of both techniques to be implemented in the study and the technical specifications for taking photographs and videos are included in the surgical technique manual.

1. Introduction:

Placenta accreta spectrum (PAS) is an increasingly frequent pathology, which is probably related to the increased rates of cesarean sections throughout the world[1]. This is a potentially dangerous condition associated with maternal risks, such as massive blood loss, pelvic organ damage (urinary tract or bowel), and occasional maternal mortality. Prenatal imaging detection was reported to have a high degree of accuracy in a cohort of women with an anterior cesarean delivery and placenta previa[2,3]. However, both ultrasound and magnetic resonance imaging have variable diagnostic precision depending on who performs the study, reporting failures in both diagnostic modalities[4]. Thus, even a quarter of patients undergoing surgery for suspected PAS end up having another diagnosis[5].

There are multiple management options, but the ideal treatment modality is unknown. The most widely used definitive treatment in the world is cesarean section - elective hysterectomy[6]. However, some investigators have reported that partial myometrial resection and uterine repair are successful in the vast majority of cases[7].

Even though there are multiple publications about conservative surgical management techniques in different populations, one of them being the partial resection of the myometrium followed by uterine repair (a technique called resective reconstructive surgery), the international management guidelines for PAS only include this alternative as an option in selected cases. Probably due to the little diffusion of the technique and the

need for specific training in it. However, something similar happens with hysterectomy for PAS.

However, something similar happens with hysterectomy for PAS. It can be thought that any gynecologist is qualified to perform a hysterectomy for PAS since he performs postpartum hysterectomy for other etiologies; This is an incorrect premise since PAS hysterectomy requires competencies only achieved after extensive training. Additionally, partial resection of the myometrium involves the same interventions necessary to perform a hysterectomy, only organized in a different way, which probably simplifies the procedure in some cases.

Since the most accepted technique worldwide is hysterectomy, and there is a belief that PAs affects the entire uterus, with no option of preserving this organ; It can be argued that partial myometrial resection is used in less severe cases of PAS and that more severe cases require a cesarean hysterectomy. Partial resection may be considered a useless strategy in severe cases. It can also be argued that the higher frequency of maternal complications associated with cesarean section hysterectomy may reflect the greater severity of the disease rather than the treatment modality itself. However, there are no reports of a direct comparison of these two surgical techniques and although the groups that use partial resection see important benefits over hysterectomy, a prospective study with an appropriate design is necessary to clarify which procedure is associated with better clinical results.

2. Theoretical framework:

Cesarean section followed by hysterectomy is the treatment choice in most centers that treat patients with PAS[8]. However, since 1998 the surgical treatment of PAS with uterine preservation has been described[9] and a series of 248 patients with PAS has recently been published, finding that uterine preservation was possible in 81% of the cases[7].

This surgical technique involves a partial myometrial resection, that is, the resection of the myometrium affected by the abnormal invasion of the placenta. In general, it is only a part of the uterus, finding the rest of the myometrium free of PAS and susceptible to conservation. The main objective of this surgical technique is not the preservation of the uterus. It seeks to improve clinical results (less bleeding, less surgical time, less risk of ureteral injury, etc.), however, the conception that it is only necessary to resect a part of the uterus that is affected by PAS (and not the entire organ), allows to obtain an additional result: the preservation of the uterus. Avoiding a hysterectomy not only allows new pregnancies in the patient but also reduces blood loss (there is a volume of blood that is drawn together with the uterus during the hysterectomy) and reduces the extent of pelvic dissection required to carry out the surgery.

Although international consensus includes partial myometrial resection among the possible management options for PAS, it is almost always considered that it should be reserved for special cases, emphasizing the need for specific training in the technique[10].

Even though hysterectomy adequately solves the problem of PAS, it exposes the patient to morbidity inherent in the extensive pelvic dissection required to isolate the uterus from the other pelvic structures prior to removal. Among these morbidities are bladder and ureteral injuries[11]. Hysterectomy makes new pregnancies impossible and has also been linked to alterations in ovarian function.

In the study carried out by Palacios Jaraquemada[7], 20% of the patients required a hysterectomy. The experience in our center shows that a hysterectomy was performed in 72% of patients between 2016 and 202012.

Taking into account that most cases of PAS (64.6 %%) are cases considered "less severe", that is, placenta accreta (not increta or percreta)[5] and that most patients (88%) have involvement of the upper part of the uterine segment or sector 1 of uterine vascularization ("S1")[13], it is easy to wonder if it is necessary to resect the entire uterus (hysterectomy) when only a portion of this organ is affected.

It has been shown that, if the placenta accreta spectrum affects the anterior wall of the uterus and a portion of healthy myometrium is preserved at least 2 cm cephalad to the cervix, it is possible to perform a partial resection of the myometrium (resecting the portion of myometrium affected by PAS) and reconstruct the remaining myometrium (free of placenta accreta), preserving the uterus[7]. Fortunately, most patients with PAS meet these requirements and are candidates for the partial myometrial resection technique[5,7].

It has also been reported that after basic training and thanks to inter-institutional collaboration facilitated by telemedicine, it is possible to safely perform the partial myometrial resection technique in centers that initially only perform hysterectomy[14]. These centers that recently use partial resection can achieve a frequency of uterine preservation in patients with confirmed PAS, between 9% and 42%. This lower frequency of conservation when comparing centers that recently use the technique and those with more time to perform this type of surgery[7], probably has to do with the experience applying this technique ("training curve").

Among the benefits of partial myometrial resection, over hysterectomy, are:

1. Preservation of fertility
2. Performing a less extensive surgery

3. Probably less blood loss
4. Total preservation of ovarian perfusion
5. Opportunity for differential treatment for cases that ultimately did not have PAS, despite a wrong prenatal diagnosis. In some patients, the diagnosis of PAS is suspected by ultrasound, but during laparotomy, it is found that they did not have this diagnosis (false positive of prenatal images). When, after fetal extraction, a hysterectomy is immediately carried out, it is possible to extract uteri that finally do not have PAS (22.6%)[5] Partial myometrial resection requires a dissection of the vesicouterine space before fetal extraction, so that the surgeon can observe the entire anterior face of the uterus, approaching in a better way the definitive diagnosis, even before extracting the baby.

Many observational studies describe good results with uterine preservation techniques. In March 2019, 25 publications on conservative surgical management in PAS were found, with more than 700 cases of successful uterine preservation[14]. All these studies were observational and retrospective, using different uterine preservation techniques.

There are many useful clinical variables to evaluate the effectiveness of a certain PAS management technique. Observational studies of single or multicenter cohorts report, among other variables, the volume of blood loss, the frequency of transfusions, the number of blood components transfused, the frequency of operative complications, the surgical time, the need for additional surgeries, the time postoperative hospitalization, etc[7,11,12,13,4,15,16]. Some of these variables are directly influenced by the clinical status of the patient before surgery or the postoperative management habits of the center where the surgery is carried out (duration of postoperative hospitalization, frequency of transfusions) and others have a frequency of very low presentation so that its analysis would demand population sizes that are difficult to manage (ureteral injuries, reoperations). Therefore, it is proposed that the volume of intra-surgical bleeding is the variable to evaluate as the primary outcome in a definitive clinical experiment.

3. Rationale

The most appropriate treatment modality for women diagnosed with PAS is uncertain, the most widely used is cesarean section followed by hysterectomy. This technique is associated with high volumes of bleeding and operative complications, such as urinary tract injuries[4]. Partial resection of the myometrium has been reported to be associated with a lower probability of surgical damage to pelvic organs[15].

This lower rate of complications may be due to a selection bias since it could be thought that at least in some patients with not very severe affectations (those with placenta accreta and affectation of the upper part of the uterine segment S1), it is possible to perform surgery less extensive (partial resection of the affected myometrium) and preserve fertility. While the most severe cases (placenta increta, percreta, or involvement of the

lower part of the uterus or sector 2 of uterine vascularization) are more frequently taken to hysterectomy.

Observational studies are unlikely to eliminate selection bias. The controversy can only be resolved by conducting a randomized controlled experiment in which women with a prenatal diagnosis of PAS are randomly assigned to undergo hysterectomy or partial myometrial resection as the intended treatment modality. This type of study would probably require a high number of patients and the participation of several hospitals that apply the same surgical technique. Considering that the international guidelines for the management of PAS make partial myometrial resection a technique reserved for a select group of patients, some centers refrain from implementing this type of technique and that there are not many centers in the world that do so practice.

The studies published to date evaluating partial myometrial resection are retrospective and observational in nature[7,14,15]. Although the patients who undergo this type of surgery have been compared with a group of women who finally underwent a hysterectomy after partial resection has been attempted[14,15],it is not possible to characterize in these publications two comparable groups (myometrial resection partial vs hysterectomy as management chosen and executed from the beginning of the surgery).

Since a "head-to-head" comparison between hysterectomy and partial myometrial resection has never been performed previously, there are insufficient data to define a sample size necessary for conducting a definitive randomized clinical trial. It is therefore necessary to initially carry out a feasibility study to verify that all the procedures outlined in the protocol (to be carried out later) are viable. This feasibility study will also allow the collection of clinical data from both arms of the study that will allow planning a future definitive randomized clinical experiment.

4. Research question:

Is it possible to recruit, randomize, intervene, and measure outcomes of interest in patients with PAS as part of a clinical experiment comparing two PAS surgical techniques (hysterectomy vs. partial myometrial resection) in a period of 24 months or less?

5. Objective:

6.1. Primary objective: To evaluate the feasibility of the parallel experimental design, the willingness to participate of eligible patients, and the outcome measures for conducting a randomized phase III clinical experiment comparing partial myometrial resection with hysterectomy in patients with PAS, carried out in 3 different centers, including Fundación Valle del Lili, in a period of 24 months.

6.2.Specific objectives:

1. To measure the proportion of eligible patients who agree to participate in this comparison.
2. To measure the percentage of screening failure.
3. To describe the confirmation of the presence or absence of placental accretenotic spectrum in each case.
4. To identify the degree of variability between the different methods of measuring intraoperative bleeding in each of the techniques.

6.3.Secondary objectives:

1. Clinical and sociodemographic characterization of the patient.
2. To identify the characteristics of the patient's current pregnancy.
3. To describe the clinical outcomes of interest in patients randomized to hysterectomy or partial myometrial resection.
4. To categorize the severity of surgical complications according to the Clavien Dindo classification.

7. Hypothesis

7.1.Primary hypothesis: It is possible to recruit, randomize, operate and follow-up patients recruited for an experiment comparing two surgical techniques in PAS (Hysterectomy Vs Partial myometrial resection) in a period of 24 months or less.

8. Outcomes measures/endpoints:

8.1.Primary endpoints:

- Proportion of eligible patients who agree to participate in the study.
- Screening failure percentage
- Percentage of patients assigned to each arm of the study.
- Percentage of patients with crossover between assigned study arms.
- Number of subjects who complete follow-up at 42 days postpartum.

8.2.Secondary endpoints:

- Maternal death
- Intra-surgical bleeding volume measured in mL.
- Blood component transfusion requirement, median transfusion of red blood cell units (RBCU)
- Compliance with at least one WHO Near Miss criterion (See Appendix 1)
- Ureteral injuries.
- Bladder injuries
- Need for surgical reoperation.
- Admission to the Intensive Care Unit.
- Days of post-operative hospital stay.
- Use of uterine tamponade with hydrostatic balloons.
- Presence of supra fascial hematoma
- Presence of postoperative ileus
- Vital status of the newborn
- Weight of the newborn

9. Methods:

9.1. **Study design:** Feasibility study of a randomized, controlled, multicenter clinical experiment on the use of partial myometrial resection vs hysterectomy.

It is expected to have the participation of 2 institutions invited and led by:

Hospital Universitario CEMIC (Buenos Aires, Argentina)- Dr José Miguel Palacios Jaraquemada.

Dr. Soetomo Academic General Hospital, Universitas Airlangga, (Surabaya, Indonesia)- Dr Rozi Aditya Aryananda

The 3 institutions will use the same protocol (they will apply the same surgical technique and carry out the same information recording activities), but the randomization will be stratified for each site to ensure the same number of participants for each arm of the study at the 3 sites.

9.2. **Study population**: Pregnant women with a prenatal ultrasound or magnetic resonance diagnosis of PAS (See Appendix 2: Definition of a suspected case of PAS), who will be taken to surgery to treat this disease at Fundación Valle del Lili and the institutions invited to participate

9.3. Study groups:

- Patients with a confirmed PAS diagnosis (See Appendix 2, Definition of confirmed PAS case) who will undergo partial myometrial resection.

  Although it has been reported that this type of surgery is viable in case of involvement of the anterior portion of the uterus, with a healthy myometrium of at least 2cm cephalad to the cervix. Our study suggests that partial myometrial resection should be attempted in all patients randomized to this intervention. Partial myometrial resection may not be feasible in some cases and the patient will receive a hysterectomy. The attempted partial myometrial resection does not imply a greater risk of bleeding for the patient, since having previously performed the vesicouterine dissection, vascular control techniques are readily available that can be applied in the event that the myometrial resection is unsuccessful, and a hysterectomy can be performed without exposing the patient to an increased risk of bleeding.

- Patients with a confirmed diagnosis of PAS (See Appendix 2, Definition of a confirmed PAS case) who will undergo hysterectomy. All patients randomized to this intervention will receive a hysterectomy, regardless of the extent or severity of injury found at laparotomy.

Both groups of patients will receive standard postoperative care (monitoring and hemodynamic, respiratory, metabolic support and in general the management described for this intervention)

9.4. Selection of participants:

Women with a previous cesarean section, anterior placenta previa, and imaging (ultrasound or MRI) with signs suggestive of PAS will be eligible to participate (See Appendix 2: Definition of a suspected PAS case). Informed consent will be requested from these patients prior to surgery. Considering that these are pregnant women, the participation of the husband or spouse will be included in the informed consent (Appendix 7). In the event that the patient does not have a husband or spouse, the "Declaration of mother head of the family" will be filled out (Appendix 8).

Randomization will be carried out before starting the surgical procedure, with the aim of reducing the possibility of selection bias by the surgical team since there is no blinding.

It is possible that some patients who are eligible before surgery and who have signed the informed consent, will cease to be eligible if macroscopic signs suggestive of PAS are not found at laparotomy (See Appendix 2: Definition of confirmed PAS case) (that is, if present a false positive result of the prenatal diagnostic images), which has been described in up to 22.6%[11] of the cases. These patients will be considered screening failures in the recruitment process and will be excluded from the statistical analysis.

9.5.1. Inclusion criteria:

- Pregnant women over 18 years of age.
- History of previous cesarean section and anterior placenta previa
- Patients with prenatal diagnosis by ultrasound or MRI of PAS (See Appendix 2: Definition of a suspected case of PAS), regardless of the suspected degree of severity of the disease.
- Requirement for surgical management of placental accreta on a scheduled basis.
- Patients without active vaginal bleeding in the period immediately before surgery (Patients entering the operating room without active bleeding).

9.5.2. Exclusion Criteria:

- Women without previous living children.

9.6. Sample size:

As the aim of the study is not to compare the effectiveness between interventions, a formal power calculation was not performed. A sample size of 60 participants. According to the estimated recruitment rate for each center, the following distribution is proposed: 36 patients from Indonesia, 12 patients from Argentina and 12 patients from Colombia to address the feasibility objectives.

9.7. Recruitment strategy:

9.7.1. Participant selection:

Women with a previous cesarean section, anterior placenta previa, signs of PAS on ultrasound or prenatal magnetic resonance imaging (See Appendix 2: Suspicious case of

PAS) and who meet the inclusion criteria will be considered as possible candidates to participate in the study. Patients will be identified by the medical group and evaluated for their eligibility at the time of hospital admission before surgery.
Once the treating medical personnel confirm the eligibility of the patient, she will be provided with complete information about the study and the physical informed consent, the patient will have at least 48 hours to evaluate it, discuss it and decide whether or not she wishes to participate.

Participants who voluntarily decide to take part in the study will not receive any payment or remuneration as a result of their participation.

Some anonymized data of the women who decline their participation in the study and that will be used in the CONSORT report will include:

Date of cesarean section.
Ethnicity
Number of living children
Reason why the patient is not eligible, or if she is eligible because she declined to participate.

Before the start of the surgical procedure, the clinical coordinator of the study will be in charge of revealing the surgical intervention to which the patient has been randomized to reduce the probability of selection bias since blinding is not possible in this study.

Once the laparotomy has been performed, the surgeon will define whether or not there are macroscopic signs on the anterior face of the uterus that confirm the diagnosis of PAS (See Appendix 2, Confirmed case of PAS). The clinical diagnostic criteria reported by the International Federation of Gynecology and Obstetrics (FIGO) will be used[17].

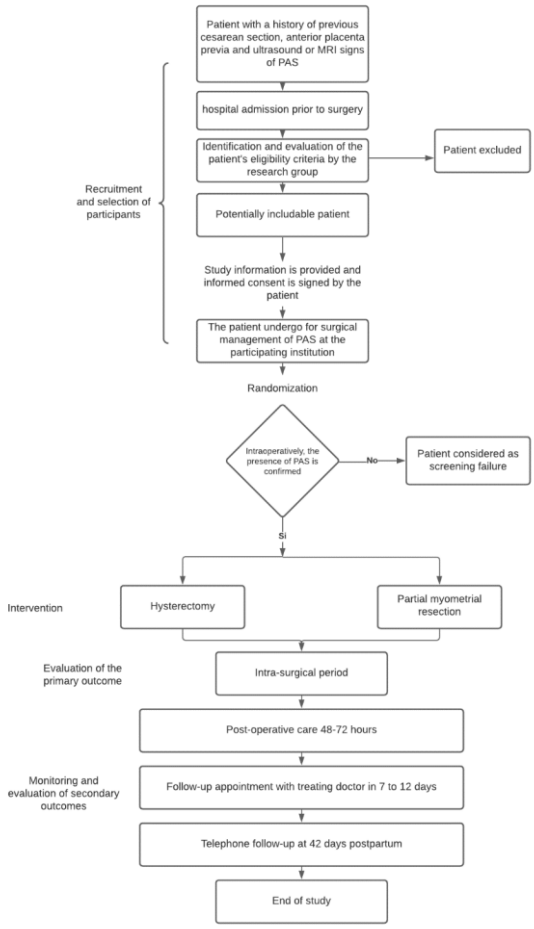
At that time, if the diagnosis of PAS is confirmed, the randomized intervention will continue. If the diagnosis of PAS is not confirmed, the patient will be considered a screening failure.

The entire process from the disclosure of the randomization, the confirmation or exclusion of PAS and the performance of the randomized intervention will be supervised by the study coordinator in each hospital.

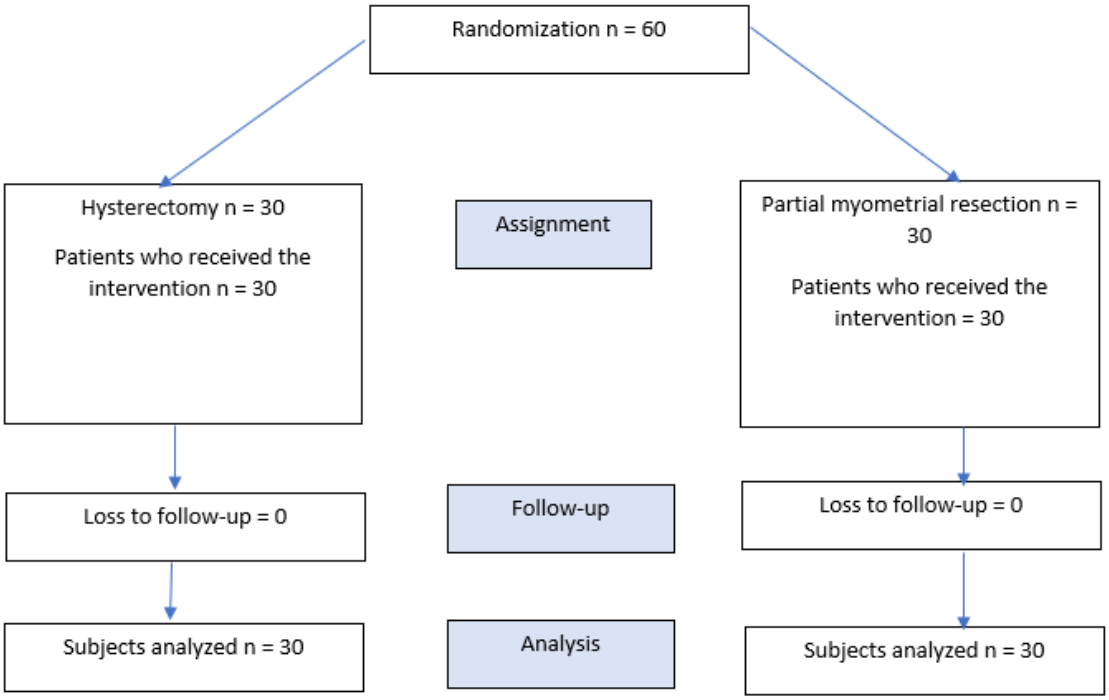
Additionally, as a quality control, all surgery will be recorded on video and photos. With special emphasis on intraoperative findings after laparotomy that confirm or rule out the diagnosis of PAS and define the continuity of the patient in the study, or the exclusion of it (in case PAS is ruled out). The photographic and video recording of the findings during laparotomy should account for the presence of the clinical criteria for PAS endorsed by FIGO[17] (See Appendix 10).

Additionally, a photo and video record will be taken of the prenatal ultrasound that suggests a diagnosis of PAS (according to the medical criteria of the investigator), as well as photos of the histological study that confirm or rule out the diagnosis of PAS. Those patients who meet all the inclusion criteria and all the exclusion criteria are discarded will finally be chosen for the study (See Appendix 2: Inclusion / Exclusion Form). Each center will be responsible for completing the information of all the participants who were not entered into the study, recording the reasons for their NOT inclusion (See Appendix 3: Summary Screening).

9.8. General flowchart of study



9.9. Randomization flowchart



9.10. Procedures flowchart

Visit number	**V1**	**V2**	**V3**	**V4**	**V5**	**Vn**
Day	D0	D1	Hasta 72h Postoperatorias	D7 a D12 Postoperatorio	D42 Postoperatorio	Visitas no programadas
Name of the visit	Selección	Aleatorización	Seguimiento 1	Seguimiento 2	Fin de Seguimiento	Seguimiento N
Activity						
Hospital admission	X					X
Inclusion and exclusion criteria	X	X				
Assignment of consecutive number (Screening)	X					
Informed consent	X					
Demographic data	X	X				

Obstetrics and gynecology history	X	X				
Short Physical Examination (Height and weight)		X				
Laparotomy / Randomization		X				
Hydrostatic balloon uterine tamponade		X	X			
Characteristics of the surgical procedure		X				
Newborn: vital status and weight		X	X			
Type of postoperative hospitalization			X			
Complication of surgery			X	X	X	X
ICU admission			X	X	X	X
Surgical reintervention			X	X	X	X
ICU discharge			X	X	X	X
Evaluation Near Miss Criteria			X	X	X	X
Blood component transfusion			X	X	X	X
Arterial thrombosis associated with vascular intervention			X	X	X	X
Ileum			X			
Supra fascial hematoma			X			
Surgical wound infection				X	X	X

Clavien Dindo Scale			X	X	X	X
Hospital discharge				X	X	X
Adverse Events		X	X	X	X	X
Telephone contact (Telemedicine)					X	

9.11. Operative aspects:

Eligible women will receive complete information about the study. If they agree to participate in it, they will sign the informed consent for both interventions: hysterectomy and partial myometrial resection. The final modality of intervention will be decided at randomization prior to the start of the surgical procedure.

The patients will undergo laparotomy with adequate anesthesia, the anesthesia method will be decided based on the pre-anesthetic evaluation and the mother's choice. During laparotomy, the clinical signs and the FIGO classification for PAS will be recorded[17]: Once the abdomen is surgically entered, the anterior aspect of the uterine segment is observed in detail (it is likely that a vesicouterine dissection will be required) and the diagnosis of PAS is confirmed (See Appendix 2, Definition of confirmed case of PAS).

If the diagnosis of PAS is ruled out (If the clinical criteria for PAS proposed by FIGO [Appendix 2] are not present), the patient is excluded from the study and subsequent surgical management will be defined by the treating surgical group.

If the diagnosis of PAS is confirmed by observing the clinical criteria endorsed by FIGO (Appendix 2), the patient's participation in the study is confirmed and the surgical procedure defined by randomization is continued, that is, one of the two arms of the study:

Primary hysterectomy: An incision will be made above the level of the placenta, delivering the newborn. Uterotonics will be administered, and spontaneous delivery of the placenta will be awaited using gentle traction. The absence of spontaneous separation of the placenta will confirm the diagnosis of PAS, the patient will undergo hysterectomy. The complete removal of the uterus will be attempted, including the cervix, the duration of the intervention and intraoperative blood loss will be recorded, as well as the damage to organs neighboring the uterus. In this arm of the study, hysterectomy will be performed in 100% of patients.

Partial myometrial resection: The technique described by Palacios-Jaraquemada et al[5]. will be followed. Briefly, the uterus will be dissected to free it from the posterior wall of

the bladder to the cervix. The vesico-uterine vessels will be ligated and the parametrial space will be visualized. The hysterotomy will be performed in the upper segment, immediately above the area of invasion of the myometrium. The entire invaded myometrium and the entire placenta will be removed. The uterus will repair itself in one or two layers. Intrauterine balloon tamponade will be used if indicated.

Post-operative care will be routine care according to the indication of the treating medical team.

To consult the detailed description of the interventions (hysterectomy and partial resection) and the procedures for the evaluation of clinical outcomes, see the standardized operating plan (See Appendix 4)

From the admission of the patient to the obstetric care unit until the end of the study follow-up process (42 days after the cesarean section), it will be evaluated whether the patient meets the criteria for extreme maternal morbidity (Consult the maternal morbidity surveillance protocol Extrema Cod: 549 of the National Institute of Health, available at: https://www.ins.gov.co/buscador-eventos/Paginas/Fichas-y-Protocolos.aspx) in case of meeting any of the inclusion criteria, the treating medical team will be in charge of filling out the individual notification form Cod. INS 549 for immediate reporting

In the same way, in the event of the death of a participant during the study period, due diligence of the individual notification form will be carried out for the maternal mortality event, INS Code 551 by the treating medical team.

9.12. Randomization:

There will be a randomization in a 1: 1 ratio in blocks of 4 and 6, stratified by each center. This process will be conducted by a statistician from the Fundación Valle del Lili Clinical Research Center independent of the research group, who will use a public access package: *Random Allocation Software* (http://www.msaghaei.com/Softwares/dnld/RA .zip) for that purpose.

The randomization sequence will rest in the *RED Cap*® software. Prior to the start of the surgical procedure, the clinical coordinator of the study will be asked to reveal the result of the randomization, once the presence of PAS is confirmed (See Appendix 2, confirmed case of PAS), the surgery will continue towards one of the two possible options (hysterectomy or partial myometrial resection). Participants and researchers will be informed of the intervention since it is an open-label clinical experiment.

9.13. Blinding:

This is an unblinded study as it is not possible to conceal the surgical procedure for each arm from the operator (Treating Physician) or from the participant.

The information of each patient will be consigned in electronic formats. In these, the therapeutic modality will not be expressly identified, in such a way that the independent statistician who will perform the analysis will also, in principle, not know the group to which each patient was assigned.

9.14. Statistical analysis plan

Statistical analysis will be performed in accordance with the principles of intention-to-treat analysis. Descriptive statistics will be used to summarize the feasibility results. According to the CONSORT guide for feasibility experiments (Eldridge et al., 016), efficacy tests are not recommended, because the study is not designed to detect differences between the types of surgery, therefore, for the clinical outcomes analyzes will focus primarily on descriptive analyzes using the mean (standard deviation) or median (interquartile range) for continuous outcomes and absolute frequencies and percentages for categorical outcomes. For the specific objective of the degree of variability of the bleeding methods, the coefficient of variation of each method within the surgical techniques will be calculated. STATA version 14.0 ® software will be used.

9.15. Interim analysis:

An interim analysis will be carried out when 10 patients have been randomized, to evaluate possible factors to improve in the execution of the study. This interim analysis will be carried out by the executing institution and the research group.

10. Data collection, patient follow-up, study monitoring and clinical outcomes:

10.1. Data collection:

A CRF ("case report form") will be designed together with the systems support staff of Fundación Valle del Lili, the clinical history will be used as the source document, from which the data of interest will be obtained to be entered into the *RED Cap*® electronic platform where the variables to be studied will be recorded and the demographic data of the participants, obstetric history (pregnancy and parity) of previous surgeries that include cesarean deliveries or uterine curettage or other gynecological surgery will be collected, gestational age at diagnosis, gestational age at delivery, and birth outcome. Prenatal complications, particularly bleeding before delivery (number of episodes and quantity, blood transfusions) will be recorded.

The type of surgical procedure, the type of anesthesia, the duration of the procedure, the

surgical details, the volume of total intra-surgical bleeding, the details of the transfusion of blood components and the surgical complications, transfer to the Intensive Care Unit (ICU), length of stay in ICU in days / hours, the WHO Near Miss criteria (Appendix 1). Postoperative complications and the total length of hospital stay will be recorded.

Information will be collected about the histopathological analysis of the surgical specimen in relation to the confirmation of the pathology and the degree of invasion described in the report.

The data collected will be stored by the executing institution and the participating institutions in the *RED Cap*® electronic platform, the main researchers of each of the participating centers will be in charge of collecting the information required in the protocol, each of them will have a profile used for the electronic entry of the information.

The information collected in this study will be recorded in a way that the subjects cannot be identified at any time. Any change in the process must be reported to the institutional review board (or Institutional Review Board IRB) of the clinical research center of Fundación Valle del Lili by the study coordinator.

This database will not have specific information on substance abuse, psychiatric disorders, sexually transmitted diseases, or identifier such as name or identity document number.

Information from health records such as diagnoses, progress notes, medications used, procedures performed, laboratory findings, radiology, etc. will be stored.

This study does not contemplate the use of any device or investigational drug, no specimens or biological samples will be collected from patients for this study.

It is important to note that, in the three institutions invited to participate, the principal investigators currently carry out several research projects on PAS. Thus, the prospective collection of clinical and paraclinical variables of interest in PAS is an established habit in each of the surgeries for this disease. The three clinical leaders from each institution have successfully completed several observational projects around PAS and have scientific publications in indexed journals. Additionally, they agree to submit to the audit of each of their research groups and to centralized surveillance by the research center of the Fundación Valle del Lili, during the execution of this project.

10.2. Follow up assessments:

The study participants will be followed up to evaluate the primary and secondary outcomes and the appearance of adverse events during 4 moments:

10.2.1. Intraoperative: The total intraoperative bleeding volume will be measured, type of anesthesia used, type of skin incision, type of uterine incision, FIGO PAS classification, use of interventional radiology, use of intraoperative cell saver ("cell saver"), duration of surgery, use of uterine tamponade with hydrostatic balloons, gender and weight of the newborn.

10.2.2. **Immediate post-operatory time**: defined as the first 48 to 72 hours after the intervention, in this period of time, the patient will be monitored in the obstetric gynecological service, where each of the secondary outcomes described will be evaluated: Maternal death, Presence of Near Miss criteria, frequency and volume of transfusion of blood components, bladder injury, ureteral injury, need for reoperation, admission to ICU, days of postoperative hospital stay, disseminated intravascular coagulation, hypovolemic shock, metabolic acidosis, urinary retention, femoral thrombosis , post-operative ileus, supra fascial hematoma.

10.2.3. **Medical appointment between 7 and 12 days:** The patient is clinically evaluated by outpatient consultation on-site or telemedicine with the treating physician who determines if any of the secondary outcomes described above have occurred and additionally if she has developed an infection of the surgical wound.

10.2.4. **Follow-up at 42 days postpartum:** the patient will be followed up by telephone when she reaches 42 days after the surgical intervention, where a general evaluation of her health will be made, and the follow-up will be terminated.

10.3.Data quality monitoring:

Both the executing institution and the institutions participating in the study will designate a person in charge of monitoring the quality of the data. In the executing institution, the person in charge will be Dr. Liliana Vallecilla, who will perform a data quality analysis of 100% of the data corresponding to the primary outcome to be evaluated and 100% for the secondary outcomes, in this analysis of quality, a review of the data entered into the system will be carried out and it will be compared with the clinical records of each institution, the process will be carried permanent and will be programed the first monitoring with each center 5 days after to first participant enrollment, the additional monitoring visits will be performed according to recruitment rate and presence of primary and secondary outcomes in participating individuals.

The two institutions invited to participate will also receive supervision from the monitor of this study at Fundación Valle de Lili, who will establish frequent communication with the coordinators of the centers in Argentina and Indonesia.

10.4. **Duration of the study:** Taking into account the frequency of cases of this pathology per year, it is estimated that each executing institution will attend 1 or 2 cases of PAS per month, with a total duration of 24 months.

10.5. Study completion: The study is considered to end for each patient 42 days after surgery when the last moment of follow-up is performed. The feasibility study ends 42 days after the cesarean section of the last randomized patient

10.6. **Withdrawal of informed consent:** The participant or their legal representative may voluntarily withdraw their consent to participate in the study for any reason and at any time. In case of withdrawal of informed consent, the usual follow-up of the patient will continue during the post-surgical period and the follow-up appointment in 7 to 12 days. The only time of the follow-up that will not be carried out will be the telephone control at 42 days postpartum. Once the informed consent is withdrawn, no further information will be collected, the information collected until the moment of withdrawal of consent will be used in the analyzes contemplated in the study.

11. Ethical considerations

The study will be submitted to the evaluation of the local ethics committee for its approval.

11.1. Risk Level (According to Resolution 8430)

This study complies with the CIOMS declarations, international human research agreements such as the Helsinki declaration and the Nuremberg code, and the national regulations of article 11 of resolution 8430 of 1993, It is considered a study with risk "greater than the minimum", since it is a study where two surgical interventions will be randomized. However, these interventions are part of the conventional and accepted therapeutic options for the management of PAS. Given the implicit risk of this study, informed consent will be requested from all patients prior to undergoing any intervention.

To ensure the confidentiality of the data, the identification variables of each patient will be coded to prevent the traceability of the identification; no one outside the research group or the ethics committee will have access to the database, and no data will be published that would allow the identification of the participants.

Before the start of the study, the approval of the ethics committee will be requested for the study protocol, the informed consent forms, and the declaration of the mother head of the household.

Substantial amendments that require review by the ethics committee will not be implemented until the committee provides a favorable opinion for the trial.

Informed consents obtained from randomized patients will be notified monthly to the ethics committee for review. The inclusion of the first participant will be notified to the committee within the first 24 hours after signing the informed consent. A semiannual report on the progress of the study will be made or sooner if this is required

The principal investigator will notify the ethics committee of the end of the study. If it is terminated prematurely, the committee will be notified explaining the reasons for the premature termination.

11.2. Consent:

According to resolution 8430 of 1993, article 14, for research on human beings, there will be written informed consent, by which the research subject or their legal representative understands and accepts their consent (Appendix 7).

To obtain informed consent to the legal representative, the following information will be provided

a) Purpose of the investigation and procedures

b) Study inclusion criteria and time of participation

c) Risks and benefits

d) Confidentiality of information

e) Payments and compensation

Informed consent will be obtained before the participant undergoing any trial-related intervention. Because this study considers a vulnerable population (pregnant women) as the reference population, the informed consent is based on resolution 8430, article 30, where it is contemplated that the informed consent of the woman and her spouse must be obtained, prior information from the possible risks for the embryo, fetus or newborn in your case. If informed consent cannot be obtained from the spouse, there will be a statement from the mother head of the family where the study participant certifies that she is economically and socially responsible for her minor children (Appendix 8).

The principal investigator retains overall responsibility for conducting research on his site, this includes obtaining informed consent from participants on his site. They must ensure that any person to whom the responsibility of participating in the informed consent process is delegated is duly authorized, trained, and competent to participate in accordance with the ethically approved protocol, the principles of Good Clinical Practice (GCP), and the Declaration of Helsinki. If a delegation of consent is acceptable, details must be provided.

The participant will remain free to withdraw at any time from the trial without giving reasons and without jeopardizing her further treatment and will be provided with a point of contact where she can obtain further information about the trial. The data collected up to the time of withdrawal will only be used after withdrawal if the participant has consented to it. Any intention to use such data will be described in the consent literature. When a participant is required to give her consent again or a participant is required to provide new information, it will be the responsibility of the principal investigator to ensure that this is done promptly.

The Principal Investigator at each site assumes responsibility for ensuring that all vulnerable participants are protected and voluntarily participate in an environment free from coercion or undue influence.

Consent will include the use of anonymous images (ultrasound or MRI), photographic and video recording of operative findings, as well as histopathology slides for independent review by blind experts.

11.3. **Conflict of interests**

The researchers of this study declare that they have no conflicts of interest.

12. Report of adverse events:

The principal investigator of each center will be responsible for managing the safety of each participant and identifying adverse events related or not to the study interventions.

Adverse events should be recorded with the following information:

- Identification of the participant in the study.
- Time from randomization to occurrence of the event.
- Identification of the possible causal relationship between the event and the surgical intervention (hysterectomy or partial myometrial resection)
- Resolution or improvement of the adverse event.

12.1.**Monitoring of adverse events:**

All adverse events (AE) that occur within the first 42 days after randomization must be reported to the respective ethics committee following the guidelines for reporting serious adverse events (SAE), maintaining the confidentiality of the information. The SAE must be reported to the committee within the first 24 hours of the event.

12.2. Definition of adverse event: An Adverse Event (AE) is considered to be any adverse medical situation in a patient or subject of a clinical investigation who was

administered a pharmaceutical product or underwent a procedure and that does not necessarily have a causal relationship with this treatment. . Therefore, an AE can be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the use of a medicinal product (research) or a certain intervention, whether or not it is related to it. product or intervention.

- Events that meet the definition of EA and their expected frequencies:
- Transfusions of more than 4 units of red blood cells (UGR):> 40%
- Bladder injury:> 60%
- Ureteral injury:> 30%
- Surgical wound infection:> 30%
- Complications related to intra-arterial balloons such as vessel thrombosis:> 30%

Events that DO NOT meet the definition of EA:

- Post-operative ileus
- Urinary retention
- Supra fascial hematoma
- Postpartum hemorrhage <2.5 L
- Expected daily fluctuations of pre-existing diseases or conditions present or detected at the beginning of the study that do not worsen.

12.3. Definition of serious adverse event (SAE)

Serious adverse event (SAE) is defined as any unfavorable occurrence that has the following characteristics:

- Cause death
- Life-threatening: "Life-threatening" corresponds to situations in which the participant was at risk of death at the time of the event.
- Requires hospitalization (hospital admission for constant observation or prolongs existing hospitalization)
- Causes a significant disability or alteration of a person to perform normal vital functions, persistent or significant disability, does not include events of minor significance such as common headache, nausea, vomiting, diarrhea, flu, accidental trauma that may interfere with normal functions of everyday life and prevent them, but they are not important events.
- Congenital anomaly / birth defect in the participant's offspring.

- Major medical events at the discretion of the principal investigator that may endanger the participant.

12.4.EA and SAE registration:

- The investigator will review all the documentation related to the adverse event and verify that it is consigned in the adverse event report form (Appendix 6).
- The investigator will determine a diagnosis based on symptoms, signs, and all clinical information. The diagnosis is the one that is recorded as an adverse event.
- In the event of serious adverse events, the principal investigator will report them to the institutional ethics committee within the first 24 hours of detecting the adverse event.
- In case of adverse events, the principal investigator will report it to the institutional ethics committee within the first month of detecting the adverse event.

12.5. Assessment of AE intensity:

The researcher will carry out an evaluation of the intensity of each AE and SAE:

Grade 1 or mild: Mild symptoms that cause minimal or no interference with social activities and usual functions with indicated intervention.

Grade 2 or moderate event: Moderate symptoms causing more than minimal interference with usual social and functional activities with indicated intervention.

Grade 3 or serious event: Serious symptoms that cause inability to perform usual social and functional activities with indicated intervention or hospitalization.

Grade 4 or life-threatening event: possibly life-threatening symptoms causing inability to perform basic self-care functions with indicated intervention to prevent permanent failure or ongoing disability or death.

Grade 5 death related to AE.

12.6. Adverse event evaluation and safety committee:

The safety committee will be integrated by:

- Methodologist / statistician: Diana Marcela Martínez
- Peer evaluator: Obstetrician gynecologist specialized in Intensive Care: Dr Juan Manuel Burgos Luna

- Obstetrician gynecologist specialized in Epidemiology: Dr Natalia Catalina Riascos Caipe

All independent of the group of researchers.

They will be in charge of monitoring the occurrence of AE and the proper conduct of the study.

12.7. **Assessment of causality**:

The safety committee will determine the probability that the protocol caused the AE. The committee may change its opinion on causation based on AE tracking information. The criteria presented below are intended to serve as a reference:

- Exposure: Proof that the participant was exposed to the product.
- Temporal evaluation: Time since the intervention in relation to the moment of the AE onset.
- Probable cause: Cause that most reasonably explains the occurrence of the AE

12.8.Protection of the safety of the participants:

As part of the management of the previously exposed medical and legal risks, Fundación Valle del Lili, will acquire a civil liability policy to ensure the safety of the participants in the event of an accident or adverse event.

13. SCHEDULE:

Activity / Year	March- April 2021	May 2021	Agust 2021- September 2023	October 2023- June 2023
1. Protocol writing	X			
Approvals				
2. Presentation of the protocol		X		
3. Methodological evaluation		X		
4. Evaluation by the FVL ethics committee		X		
Execution				
5. Data collection			X	

6. Analysis of the information				X
Socialization of Results and Reports				
7. Manuscript writing				X
8. Poster presentation				X
9. Manuscript submission				X
10. Article publication				X

14. BUDGET

The two surgical options contemplated in this study are procedures performed routinely in participating hospitals. They are also part of the management options contemplated in the international PAS management guidelines. The costs of the surgery will be assumed by the insurers (medical insurance company) of each patient who, even before the execution of this project, include both surgical management options (hysterectomy and partial myometrial resection) among the benefits contracted with the participating hospitals.

The proposed methodology does not include the addition or subtraction of any input or surgical procedure to the usual medical practice in hospitals, in this way the costs of care for hospitals will not be modified.

The time allocated to this study by the researchers and coordinators in each participating hospital will be assumed by the principal investigator or the institution that in each country will assume the research agreement with Fundación Valle del Lili.

Titulo propuesta de investigación	
HISTERECTOMÍA VS RESECCIÓN PARCIAL MIOMETRIAL PARA EL MANEJO DEL ESPECTRO DE ACRETISMO PLACENTARIO (EAP). ESTUDIO DE FACTIBILIDAD DE UN EXPERIMENTO CLÍNICO ALEATORIZADO CONTROLADO (RCT-PAS)	
Fecha Elaboración:	12/08/2021
Código de creación:	ACAD-019-2021

Rubro	Financiado	Contrapartida		Valor Total
		Efectivo	Especie	
Personal de Apoyo	$ -	$ -	$ 72.240.000	$ 72.240.000
Compra de Equipos	$ -	$ -	$ 6.246.795	$ 6.246.795
Laboratorios Clínicos y Ayudas Diagnosticas	$ -	$ -	$ 1.185.030.000	$ 1.185.030.000
Servicios técnicos	$ 2.824.580	$ -	$ -	$ 2.824.580
Materiales e insumos	$ 700.000	$ -	$ -	$ 700.000
TOTAL	**$ 3.524.580**	**$ -**	**$ 1.263.516.795**	**$ 1.267.041.375**

15. VARIABLES:

Feasibility variables				
Variable	**Definition**	**Tipe of variable**	**Operative leve**	**Outcome measure**
Women who participated in the study	Number of women who agreed to participate in the study	Continuous quantitative	Number	Frequency and percentages
Screening Failure	Number of women who had suspected PAS by ultrasound or magnetic resonance, agreed to participate in the study, but intraoperatively the diagnosis of PAS was ruled out (False positive)	Continuous quantitative	Number	Frequency and percentages
Number of subjects randomized per month	Number of women who agreed to participate in the study and were randomized to one of the arms of the study	Continuous quantitative	Number	Frequency and percentages
Randomization arm	Arm to which the patient was assigned	Qualitative nominal	1.Hysterectomy 2. Partial myometrial resection	Frequency and percentages
Surgical intervention performed	Surgical intervention performed to each participant	Qualitative nominal	1.Hysterectomy 2. Partial myometrial resection	Frequency and percentages
Patients completing follow-up	Number of patients who complete follow-up up to 42 days postpartum	Continuous quantitative	Number	Frequency and percentages

Sociodemographic characteristics				
Variable	**Definition**	**Tipe of variable**	**Operative leve**	**Outcome measure**
Maternal age	Age of the patient at the time of care for the obstetric event	Continuous quantitative	Number (Years)	Tendency and dispersion
Weight	Weight in Kg	Continuous quantitative	Number (Kg)	Tendency and dispersion
Height	Height in cm	Continuous quantitative	Number (cm)	Tendency and dispersion
Body mass index	Patient kilograms over square meters	Continuous quantitative	Number	Tendency and dispersion
Gravity	Number of pregnancies the	Continuous quantitative	Number	Tendency and dispersion

	patient has had, counting the current			
Parity	Number of previous deliveries of the patient at the time of care	Continuous quantitative	Number	Tendency and dispersion
Previous Abortions	Number of abortions the patient has had at the time of care	Continuous quantitative	Number	Tendency and dispersion
Previous caesarean sections	Number of previous cesarean sections the patient has had at the time of care	Continuous quantitative	Number	Tendency and dispersion
Previous Dilation & curettage	Number of previous curettage	Continuous quantitative	Number	Tendency and dispersion
Previous myomectomies	Number of previous myomectomies	Continuous quantitative	Number	Tendency and dispersion

Characteristics of the current pregnancy				
Variable	**Definition**	**Tipe of variable**	**Operative leve**	**Outcome measure**
Gestational age at the time of diagnosis of PAS	Gestational age at the time of diagnosis of PAS	Continuous quantitative	Number	Tendency and dispersion
Diagnostic method of PAS	The diagnosis of PAS was made by ultrasound or MRI	Qualitative nominal	1.Ultrasound 2.Magnetic Resonance 3. Ultrasound and Magnetic Resonance	Frequency and percentages
Vaginal bleeding during the first trimester of pregnancy	Presence of vaginal bleeding during the first trimester of pregnancy	Qualitative nominal	0.NO 1. YES	Frequency and percentages
Presence of antepartum hemorrhage	Did the patient have vaginal bleeding before delivery?	Qualitative nominal	0.NO 1. YES	Frequency and percentages
Antepartum hemorrhage volume	Volume of bleeding before delivery	Continuous quantitative	Number (Milliliters)	Tendency and dispersion
Diagnosis of hypertensive disorder	The patient has a diagnosis of some type of hypertensive disorder during pregnancy	Qualitative nominal	0.NO 1. YES	Frequency and percentages
Diagnosis of Gestational Diabetes	The patient is diagnosed with diabetes during pregnancy	Qualitative nominal	0.NO 1. YES	Frequency and percentages

Surgical features

Variable	Definition	Tipe of variable	Operative leve	Outcome measure
Screening failure	Screening failure for false positive diagnosis of PAS	Qualitative nominal	0.NO 1. YES	Frequency and percentages
Gestational age at birth	Semanas y días a los cuales se dio el nacimiento	Continuous quantitative	Number	Tendency and dispersion
Type of anesthesia used in the surgical procedure	Type of anesthesia used during the surgical management of PAS	Qualitative nominal	1. Neuraxial 2.General 3. Neuraxial with conversion to general	Frequency and percentages
Type of skin incision	What type of skin incision is made during the surgical management of PAS	Qualitative nominal	1. Vertical 2. transverse	Frequency and percentages
Type of uterine incision	What type of uterine incision is made during the surgical management of PAS	Qualitative nominal	1. Upper uterine segment 2. Lower uterine segment 3. Fundic	Frequency and percentages
FIGO PAS Classification	Categories described by FIGO of the EAP	Qualitative ordinal	0. Grade 1 1. Grade 2 2. Grade 3A 3. Grade 3B 4. Grade 3C	Frequency and percentages
Topographic classification of the PAS	Topographic classification of placental accreta	Qualitative nominal	1.S1 2. S2	Frequency and percentages
Classification according to Palacios Jaraquemada	Classification into 4 groups described by Jaraquemada palacios in 2020	Qualitative ordinal	1. Tipe 1 2. Tipe 2 3. Tipe 3 4. Tipe 4	Frequency and percentages
Use of vascular interventions	What type of vascular intervention was used during the surgical management of PAS	Qualitative nominal	1.None 2. Ligation of internal iliac arteries 3. Endovascular occlusion of the internal or common iliac arteries (balloons) 4.Clamping or ligation of the aorta 5. Aortic endovascular occlusion (Balloon) 6. Manual compression of the aorta	Frequency and percentages
Use of cell saver	Cell saver was used during the surgical management of PAS	Qualitative nominal	0.NO 1. YES	Frequency and percentages
start surgery hour	**Start surgery hour**	NA	Hours and minutes	
End surgery hour	**End surgery hour**	NA	Hours and minutes	
Duration of surgery	Duration of the surgical procedure in min	Qualitative nominal	Number	Tendency and dispersion
Hystological confirmation of PAS	Hystopathology reports a excluyent or confirmative diagnosis of PAS	Qualitative nominal	0. NO 1. YES 2. NON AVAILABLE HYSTOPATHOLOGY	Frequency and percentages

PAS invasión degree related with hystopathology	Most high degree of PAS according **hystopathology**	Qualitative nominal	0. Accreta 1. Inccreta 2. Percreta	Frequency and percentages

Clinical outcomes				
Variable	**Definition**	**Tipe of variable**	**Operative leve**	**Outcome measure**
Intra-surgical bleeding volumen for pads stimation	Total blood loss during the procedure for pads calculation	Continuous quantitative	Number	Tendency and dispersion
Intra-surgical bleeding volumen for suction stimation	Total blood loss during the procedure for suction calculation	Continuous quantitative	Number	Tendency and dispersion
Intra-surgical bleeding volumen for Reolecting bag stimation	Total blood loss during the procedure for recollecting bag calculation	Continuous quantitative	Number	Tendency and dispersión
Intra-surgical bleeding volumen	Total blood loss during the procedure	Continuous quantitative	Number	Tendency and dispersion
Hospital admission date	Hospital admission patient date	NA	Day/month/year	NA
Hospital discharge date	Hospital discharge patient date	NA	Day/month/year	NA
Numbers of day in-hospital	Total numbers of day in-hospital	Continuous quantitative	Number	Tendency and dispersion
Numbers of day of postoperative stay at hospital	Total numbers of day of postoperative stay at hospital	Continuous quantitative	Number	Tendency and dispersion
Admission to intensive care unit (ICU) related whit PAS	The patient was admitted to the intensive care unit	Qualitative nominal	0. NO 1. YES	Frequency and percentages
ICU admission date related whit PAS	ICU admission date	NA	Day/month/year	NA
ICU discharge date related whit PAS	ICU discharge date	NA	Day/month/year	NA
Number of days of ICU stay related whit PAS	Number of days of post-operative stay in ICU	Qualitative nominal	Número (días)	Tendency and dispersion
Presence of at least 1 Near Miss criterion	The patient meets the WHO Near Miss criteria (Appendix 1)	Qualitative nominal	0. NO 1. YES	Frequency and percentages
Blood component transfusion	Was the patient transfused with any blood components?	Qualitative nominal	0. NO 1. YES	Frequency and percentages

Number of Units of red blood cells transfused	Number of Units of Red Blood Cells transfused	Continuous quantitative	Number	Tendency and dispersion
Number of Units of fresh plasma transfused	Number of Units of fresh plasma transfused	Continuous quantitative	Number	Tendency and dispersion
Number of units of platelets transfused	Number of units of platelets transfused	Continuous quantitative	Number	Tendency and dispersion
Number of Cryoprecipitate Units transfused	Number of Cryoprecipitate Units transfused	Continuous quantitative	Number	Tendency and dispersion
Administration of lyophilized fibrinogen	Was the patient given lyophilized fibrinogen?	Qualitative nominal	0. NO 1. YES	Frequency and percentages
Use of uterine tamponade with hydrostatic balloons	Use of hydrostatic balloons for uterine tamponade	Qualitative nominal	0. NO 1. YES	Frequency and percentages
Bladder injury	The patient presented bladder injury during the surgical management of PAS	Qualitative nominal	0. NO 1. YES	Frequency and percentages
Ureteral injury	The patient presented ureteral injury during the surgical management of PAS	Qualitative nominal	0. NO 1. YES	Frequency and percentages
Intestinal injury	The patient presented intestinal injury during the surgical management of PAS	Qualitative nominal	0. NO 1. YES	Frequency and percentages
Need for surgical reintervention	The patient needed surgical reintervention	Qualitative nominal	0. NO 1. YES	Frequency and percentages
Arterial thrombosis related whit vascular interventions	The patient presented arterial thrombosis during the postoperative period	Qualitative nominal	0. NO 1. YES	Frequency and percentages
Post operative ileus	The patient presented ileus during the postoperative period	Qualitative nominal	0. NO 1. YES	Frequency and percentages
Supra fascial hematoma	The patient presented a supra-fascial hematoma in the post-surgical period.	Qualitative nominal	0. NO 1. YES	Frequency and percentages
Surgical wound infection	The patient had a surgical wound infection in the 30	Qualitative nominal	0. NO 1. YES	Frequency and percentages

	days after the procedure			
Maternal death	Maternal death of patient during study period	Qualitative nominal	0. NO 1. YES	Frequency and percentages
Clavin Dindo complications classification	Complications classification according Clavin Dindo	Qualitative nominal	0. Grade I 1. Grade II 2. Grade IIIa 3. Grade IIIb 4. Grade IVa 5. Grade IVb 6. Grade V	Frequency and percentages
Newborn status	El recien nacido tenía algún signo de vida al momento del nacimiento	Qualitative nominal	0. live 1. Dead	Frequency and percentages
Newborn weight	Newborn weight in grams	Continuous quantitative	Number	Tendency and dispersion

16. TABLES:

Table 1: Sociodemographic characteristics

	Total, n=60	**Group 1: Hysterectomy**	**Group 2: partial myometrial resection**
Maternal age (Median IQR)			
Body mass index (Median IQR)			
Gravity (Median IQR)			
Parity (Median IQR)			
Previous abortions (Median IQR)			
Number of previous cesarean sections (Median IQR)			
Number of previous curettage			
Number of previous myomectomies			

Tabla 2: Characteristics of the current pregnancy

	Total, n=60	Group 1: Hysterectomy	Group 2: partial myometrial resection
Gestational age at diagnosis of PAS (Median IQR)			
Diagnostic method of PAS			
Ultrasound %			
Magnetic Resonance %			
Ultrasound and Magnetic resonance %			
Presence of vaginal bleeding in the 1st trimester of pregnancy %			
Presence of antepartum hemorrhage %			
Antepartum hemorrhage volume (Median IQR)			
Diagnosis of gestational diabetes %			
Diagnosis of hypertensive disorder of pregnancy %			

Tabla 3: Características del nacimiento

	Total, n=60	Group 1: Hysterectomy	Group 2: partial myometrial resection
Gestational age at birth (Median IQR)			
Type of anesthesia used in the procedure %			
Neuraxial			
General			
Neuraxial with conversion to general			
Type of skin incision			
Transverse%			
Vertical %			
Type of uterine incision			
Upper segment			
Lower segment			
Fundic			
FIGO Classification for PAS			
Grade 1			
Grade 2			
Grade 3 A			
Grade 3B			
Grade 3C			
Topographic classification of PAS			
S1 %			
S2%			

Classification according to Palacios Jaraquemada			
Type 1			
Type 2			
Type 3			
Type 4			
Use of vascular interventions			
Use of cell saver			
Duration of surgery			
PAS confirmation for hystopathology			
Ivasion grade of PAS for hystopathology			

Tabla 4: Clinical outcomes

	Total, n=60	**Group 1: Hysterectomy**	**Group 2: partial myometrial resection**
Total volume of intra-surgical bleeding			
Admission to ICU %			
Number of days of ICU stay (Median IQR)			
Patient meets Near Miss criteria%			
Blood component transfusion% %			
RBCU transfused (Median RIC)			
FPU transfused (Median RIC)			
CPU transfused (Median RIC)			
Fibrinogen administration %			
Use of hydrostatic plugging with balloons %			
Bladder Injury %			
Ureteral Injury %			
Intestinal injury %			
Need for surgical reintervention %			
Arterial thrombosis %			
Post operative ileus %			
Supra fascial hematoma %			
Surgical wound infection %			
Surgical complications according Clavin Dindo classification			
Newborn status			
Newborn Weight			

Table 5: Coefficient of variation (%CV) of bleeding measures methods

Bleeding measures methods	Hysterectomy	Partial myometrial resection
Intra-surgical bleeding volumen for pads stimation	%CV	%CV
Intra-surgical bleeding volumen for suction stimation	%CV	%CV
Intra-surgical bleeding volumen for Reolecting bag stimation	%CV	%CV

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18. APPENDIX

Appendix 1: Near Miss Criteria

Clinical criteria	
Acute cyanosis	Loss of consciousness lasting ≥12 hours
Gasping	Loss of consciousness AND absence of pulse/heart beat
Respiratory rate >40 or <6/min	Stroke
Shock	Uncontrollable fit/total paralysis
Oliguria non-responsive to fluids or diuretics	Jaundice in the presence of pre-eclampsia
Clotting failure	
Laboratory-based criteria	
Oxygen saturation <90% for ≥60 minutes	Acute thrombocytopenia (<50 000 platelets)
pH <7.1	Bilirubin>100 mmol/l or > 6.0 mg/dl
PaO2/FiO2 <200 mmHg	Loss of consciousness AND the presence of glucose and ketoacids in urine
Lactate >5 mmol/l	
Creatinine ≥300 mmol/l or ≥3.5 mg/dl	
Management-based criteria	
Use of continuous vasoactive drugs	Dialysis for acute renal failure
Intubation and ventilation for ≥60 minutes not related to anaesthesia	Transfusion of ≥5 units red cell transfusion Cardio-pulmonary resuscitation (CPR)
Hysterectomy following infection or haemorrhage	

APPENDIX 2: DEFINITION OF SUSPECT AND CONFIRMED CASE OF PAS:

1. DEFINITION OF SUSPECT CASE OF PAS BY ULTRASOUND:

Presence of any of the following ultrasound findings:

1.1 Loss of the retroplacental hypoechoic line: Loss or irregularity of the hypoechoic plane between the myometrium and the placental border "Clear Zone".

1.2 Presence of abnormal placental lagoons: Presence of numerous lagoons including some long and irregular or with presence of turbulent flow.

1.3 Bladder wall disruption: Loss or disruption of the bladder wall (hyper echoic band or line between the uterine serosa and the bladder lumen).

1.4 Myometrial thinning: Myometrial thinning <1mm or undetectable.

1.5 Placental bulge: Deviation of the serosa from the expected plane, caused by an abnormal bulge of placental tissue to neighboring organs, typically the bladder. The uterine serosa appears intact, but its contour is irregular.

1.6 Focal exophytic mass: Placental tissue that surpasses the uterine serosa and extends beyond it, often seen within the full bladder.

1.7 Uterus-vesical hypervascularization: large amount of Doppler signal between the myometrium and the posterior bladder wall, this sign probably indicates numerous tortuous vessels in this region.

1.8 Subplacental hypervascularization: large amount of Doppler signal in the placental bed.

1.9 Bridging vessels: vessels that apparently extend from the placenta and cross the myometrium and beyond the serosa to the bladder or other organs.

1.10 Vessels that feed the placental lagoons: vessels with high flow velocity that feed the placental lagoons causing turbulence at their entrance.

1.11 3D intraplacental hypervascularization: abnormal placental vessels, with tortuous courses and various gauges.

2. DEFINITION OF SUSPECT CASE OF PAS BY MAGNETIC RESONANCE:

Presence of any of the following ultrasound findings:

2.1 Hypointense bands in T2: One or more areas of hypo intensity in T2, usually with a linear configuration and in contact with the maternal surface of the placenta.
2.2 Placental bulging: Deviation of the uterine serosa from the expected plane, caused by abnormal bulging of placental tissue to adjacent organs.
2.3 Loss of the hypointense interface in T2: loss of the dark line behind the placental bed in T2 images.
2.4 Myometrial thinning: Thinning of the myometrium that covers the placenta less than 1mm or even invisible.
2.5 Bladder wall disruption: Hypointense bladder wall irregularity or disruption, which may be accompanied by blood products in the bladder lumen.
2.6 Focal exophytic mass: Placental tissue that surpasses the uterine serosa and extends beyond it, frequently seen within the full bladder and lateral to the parametrium.
2.7 Abnormal vascularization of the placental bed: prominent vessels in the placental bed with disruption of the uteroplacental interface, can extend to the myometrium to a variable degree, reaching the uterine serosa and can be accompanied by extensive neovascularization around the bladder, uterus and the vagina.
2.8 Placental heterogeneity: Heterogeneous signals in the placenta that can be seen on T1 and T2.
2.9 Asymmetric thinning of the placenta: Part of the placenta, the portion that is involved with PAS and usually the part that covers the internal cervical os (in cases of placenta previa) are asymmetrically thinned compared to the rest of the placental tissue .
2.10 Placental ischemic infarction: In the acute phase, areas of hyperintensity in T2 and hypo intensity in T1 are present, areas of placental asymmetry are described in chronic infarcts.
2.11 Abnormal intraplacental vascularization: Abnormal, tortuous and elongated vessels in T2 deep in the placenta.

3. DEFINITION OF PAS CONFIRMED CASE:

Confirmed case in Placenta Acreta laparotomy: The patient meets any of the following criteria:

- No placental separation with the administration of oxytocin and controlled cord traction.
- Attempts to remove the placenta result in heavy bleeding from the placental bed.
- Macroscopically, the uterus does not show an obvious placental bulge, no placental tissue is seen invading the surface of the uterus, and there is minimal or no neovascularization.

Confirmed case in laparotomy of Placenta increta: The patient meets any of the following criteria:
- Abnormal macroscopic findings in the placental bed, bluish or purplish color, presence of placental bulge.
- Increased Hypervascularization (Multiple vessels run parallel craniocaudal in the uterine serosa)
- No placental tissue is observed invading through the uterine serosa.
- Cord traction results in outward uterine traction without achieving placental separation.

Confirmed case in Placenta Percreta laparotomy: The patient meets any of the following criteria:

Placenta percreta grade 3A: Limited to the serosa:
- Abnormal macroscopic findings on the surface of the uterine serosa, the placental tissue invades through the surface of the uterus.
- It does not invade any organs, including the posterior bladder wall (there is a clear surgical plane between the uterus and the bladder)

Placenta percreta grade 3B: With invasion of the bladder wall:
- There are placental vessels that invade the bladder surface but not other organs.
- A clear plane between the bladder and the uterus cannot be identified

Placenta percreta grade 3C: With invasion of other pelvic organs:
- Placental vessels invade the round ligament, vaginal wall, lateral pelvic walls, or other pelvic organ (with or without invasion of the bladder)

APPENDIX 3

Inclusion and exclusion format
Institution: _____
Clinic history: _____
Screening number:

Inclusion and exclusion criteria__ __

	Inclusion criteria	**Yes**	**No**
1	Pregnant woman over 18 years of age		
2	History of previous cesarean section and previous placenta previa		
3	Prenatal ultrasound or magnetic resonance diagnosis of PAS. (Appendix 2, Suspected case of PAS) regardless of the suspected degree of severity of the disease.		
4	Requirement for surgical management of placental accreta on a scheduled basis.		
5	Patients without active vaginal bleeding in the period immediately prior to surgery (Patients entering the operating room without active bleeding).		

	Exclusion criteria	**Si**	**No**
1	Woman without children or newborns		

Elegible patient	**Si**	**No**

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Appendix 4

Screening summary
Institution: _____

	Sitio 01-FVL- SCREENING SUMMARY_ RCT-PAS Study						
	Identification				**Partipation**		**Not participating causes (number according to list)**
	Date	Age	Name	ID	If Patient is elegible	If Patient is not elegible	
					Asigned numer (Group 186)	Asigned numer (Group 189)	
1							
2							
3							
4							
5							
6							
7							
8							

Not partipating causes	
1	Some exclusion criteria
2	Denial of consent

APPENDIX 5. STANDARDIZED OPERATIONAL PLAN

All study participants will have specific roles listed below.

Principal investigators at each center:

- Albaro José Nieto Calvache. Fundación Valle del Lili (Cali, Colombia)

- Rozi Aditya Aryananda. Dr. Soetomo Academic General Hospital, Universitas Airlangga, (Surabaya, Indonesia)

- José Miguel Palacios Jaraquemada. CEMIC University Hospital (Buenos Aires, Argentina)

Roles of the Principal Investigators:

1. Design of the study protocol, construction of documents necessary to meet the requirements of regulatory committees at Fundación Valle de Lili and other participating hospitals.

2. Identify candidate patients to participate in the study. Assess your eligibility using inclusion and exclusion criteria.

3. Notify all study participants of the identification of a potentially eligible study subject. A virtual chat will be used on the Microsoft Teams® platform where all the participants will find out when each of the three participating centers identifies a potential subject to be included.

4. Provide the patient with sufficient and clear information so that she can evaluate her potential participation in the study.

5. Obtain informed surgical and study consent including hysterectomy and partial myometrial resection options.

6. Provide the study coordinator with the informed consents collected to be stored as part of the confidential study documentation.

   When the first subject of the study is admitted, the principal investigator will provide the study coordinator with the informed consent completed within the first 24 hours after collection, in order to report it to the research ethics committee. For the other participants included, the principal investigator will have up to 1 week to provide consent to the coordinator for them to be reported to the ethics committee within the first 5 days of each month

7. Convene the study coordinator before starting the surgical intervention to reveal the result of the randomization and assign one of the two possible surgical procedures. The intervention will depend on the randomization according to the sequence that resides in the Red Cap® software

8. Confirm or rule out the diagnosis of PAS by observing clinical criteria during laparotomy:
    a. To perform laparotomy and before performing hysterotomy (opening the uterus), confirm the presence of clinical signs of PAS on the anterior surface of the uterus. The presence of the signs described by the consensus of the International Federation of Gynecology and Obstetrics (FIGO), described in Appendix 2, will be sought. Definition of confirmed case.
    b. If the presence of clinical signs of PAS is confirmed, the patient continues in the study and the surgical procedure previously defined by the randomization process will be performed.
    c. If the presence of clinical signs of PAS is ruled out, the patient is excluded from the study and subsequent surgical management will be defined by the group of treating surgeons.

9. Apply the selected surgical technique in the randomization process (hysterectomy or partial myometrial resection)

    A. Total abdominal hysterectomy: An incision will be made above the level of the placenta, extracting the newborn. Uterotonics will be administered and spontaneous delivery of the placenta will be awaited using gentle traction. The absence of spontaneous separation of the placenta will confirm the diagnosis of PAS, the patient will undergo hysterectomy. The complete removal of the uterus will be attempted, including the cervix, the duration of the intervention and intraoperative blood loss will be recorded, as well as the injury to organs neighboring the uterus. In this arm of the study, hysterectomy will be performed in 100% of patients.

    B. Partial myometrial resection: The technique described by Palacios-Jaraquemada et al.5 will be followed. Briefly, the uterus will be dissected to free it from the posterior wall of the bladder to the cervix. The vesico-uterine vessels will be ligated and the parametrial space will be visualized. The hysterotomy will be performed in the upper segment, immediately above the area of invasion of the myometrium. The entire invaded myometrium and the entire placenta will be removed. The uterus will repair itself in one or two layers. Intrauterine balloon tamponade will be used if indicated

10. Carry out the prospective collection of all clinical variables during surgery.

The objective measurement of the operative sac is the variable of greatest interest in a possible controlled clinical trial and requires special description since its correct measurement is basic for the analysis of results in both arms of the feasibility study and for the planning of a subsequent study.

Objective measurement of the total intraoperative bleeding volume will be performed by 3 means:

A. **Quantification of bleeding present in intraoperative suction devices:** The surgical team will make a visible mark on the suction devices at the time of initiation of surgery. The volume that the amniotic fluid will occupy in said devices will be taken into account. To this end, before performing the hysterotomy, the surgeon will notify the anesthesia and nursing team to make an additional mark on the suction device. Similarly, when the baby and all the amniotic fluid have been extracted, the surgeon will again notify the anesthesiology and nursing team, to make a new visible mark on the suction device.

   A record will be kept of any volume of sterile solutions used to irrigate the operative field (saline, lactate Ringer). This volume will be subtracted from the final volume count, to avoid overestimating the bleed.

B. **Weight quantification of blood-soaked compresses:** Cleaning of the operative field with a compress will be preferred and not with suction devices. The blood-soaked compresses will be removed from the operative field and stored in a sterile container in case intraoperative cell recovery is required. At the end of the surgery, the weight of the soaked compresses will be performed and from the value obtained, the "dry weight" will be subtracted from the number of quantified compresses. The surgical team will previously know the weight of each compress used in your institution

C. **Quantification of vaginal bleeding with a calibrated collection bag:** All participating centers will use a blood collection bag that will be placed under the perineum of the patient before starting the surgery. This bag has a system for

measuring the volume collected that will be quantified at the end of the surgery. The Brass V® brand collection bags will be provided by the executing institution and sent to the participating institutions to ensure the standardization of vaginal bleeding measurement.

At the end of the surgery, an objective estimate of bleeding will be made by adding the volume of bleeding from the suction devices, that of the compresses and that of the vaginal bleeding collection bag.

The three participating centers will use the same blood loss measurement protocol. A member of the surgical team will be assigned to perform bleeding measurements during surgery and immediately after the procedure. Visual estimation of bleeding will not be used as it has been shown that it is not a reliable measure since it usually underestimates losses.

11. Obtain photos and videos of the surgical procedure clearly showing the presence or absence of PAS.
12. Carry out clinical follow-up during the postoperative period according to the usual PAS management protocols in each institution.
13. Carry out postoperative assessment at an outpatient check-up appointment or telemedicine in 7 to 12 days.
14. Make the follow-up call 42 days after surgery.
15. Record all the study variables in the Case Report Form (CRF) designed in the Red Cap® virtual platform within a period between 48 hours and no more than 7 days after the surgery has been performed.
15. Report identified adverse events monthly to the research ethics committee.
16. Report serious adverse events to the research ethics committee within the first 24 hours of the event.

17. Heed the recommendations of the safety and evaluation committee for adverse events.
18. Heed the recommendations of those in charge of data quality monitoring
19. Participate in the analysis of the information collected
20. Participate in the writing of the article resulting from the study.

Study coordinators and data quality monitors, Co- Investigators:

- Stiven Ernesto Sinisterra Díaz. Fundación Valle del Lili (Cali, Colombia)
- Nareswari Imanadha. Dr. Soetomo Academic General Hospital, Universitas Airlangga, (Surabaya, Indonesia)
- Fernando Paesani. CEMIC University Hospital (Buenos Aires, Argentina)

Functions of the study coordinator:

1. Support the principal investigator in the design of the study protocol and the documentation corresponding to the study.
2. Support the principal investigator in submitting the documentation corresponding to the study before the ethics committee in biomedical research within the established deadlines.
3. Respond to any request by the Center for Clinical Research or the ethics committee in biomedical research, related to the study.
4. Support the principal investigator in the process of recruiting and evaluating the eligibility of potential study participants.
5. Provide the main researcher with the printed paperwork of the documentation that must be filled out during the study.
6. Verify that the procedure for obtaining informed consent from the research subject is done correctly by the principal investigator.
7. Safeguard the informed consents filled out as part of the confidential documentation of the study, if required.
8. Report to the ethics committee in biomedical research the inclusion of the first participant in the study within the first 24 hours of their inclusion with their respective informed consent.
9. Report to the ethics committee in biomedical research within the first 5 days of each month, the duly filled informed consents.
10. Be attentive to the call from the principal investigator advising the start of surgery to reveal to the surgical team the randomized intervention assigned to the patient. This procedure will be performed in person when possible, if the presence in the surgery room of the study coordinator or the quality monitor is not possible, a video call will be used in which the result of the test will be transmitted to the surgical group. randomization, before starting surgery

11. Support the principal investigator in the prospective collection of study variables within surgery, also support the subsequent registration of it in real time (within 24 hours) in the CRF of the Red Cap® virtual platform within maximum 7 days after surgery.
12. Support the principal investigator in the echography photos of prenatal diagnosis of PAS and the histology specimens photos collection.
13. Receive and respond to observations made by the data quality monitor of the other participating institutions.
14. Monitor the follow-up process of each of the randomized subjects in the event of any adverse event or serious adverse event to make their respective report to the ethics committee in biomedical research. (serious adverse events within the first 24 hours of occurrence and adverse events monthly)
15. In the event of serious adverse events, coordinate the meetings of the adverse event evaluation committee with the principal investigator.
16. In the event of any modification to the protocol or to the documentation corresponding to the study (Appendixes, informed consent or declaration of the mother of the head of the family), submit these changes in the form of an amendment to the ethics committee in biomedical research.
17. Support the main researcher in the writing and submission of the article resulting from the study.
18. Ensure that all study procedures are carried out in accordance with the provisions of the protocol and what is approved by the ethics committee in biomedical research of Fundación Valle del Lili.

Data quality monitor functions:

1. Weekly they will evaluate compliance with the registration of the information of the patients included in the CRF of the Red Cap® platform

2. Evaluate that the information recorded for each patient included is complete and that there are no missing data.

3. They will carry out a monthly review of the quality of the information collected, comparing the data registered in the CRF and the database, with the clinical history of the patients in each institution, this will be done in 100% of the data related whit primary outcomes and 100% of the data related whit secondary outcomes.

4. They will report the findings found in the monitoring of the data to the study coordinator at the executing institution.

5. They will provide feedback to the principal investigators on their performance in registering the data on the Red Cap® platform in case of finding inconsistencies in the data.

Serious adverse event evaluation and safety committee:

Methodologist / statistician: Andrea Valencia

Peer evaluator: Obstetrician gynecologist specialized in Intensive Care: Dr Juan Manuel Burgos Luna

Obstetrician gynecologist specialized in Epidemiology: Dr Natalia Catalina Riascos Caipe

All independent of the group of researchers.

This committee is in charge of monitoring the occurrence of adverse events in study participants, ensuring their safety.

1. Depending on the rate of patient recruitment, the safety committee will hold periodic meetings to evaluate each of the serious adverse events presented during the analysis period.

2. The safety committe will be in charge of determining if the study will be stopped according whit the frequency of adverse events is higher than expected or if a serious adverse event occurs and the ethics committee will be consulted about its continuation.

3. Evaluate the causality of serious adverse events.

4. Evaluate the intensity of serious adverse events.

5. The peer evaluator and the obstetrician gynecologist specializing in epidemiology will carry out an evaluation of the possible clinical events that will contribute to the occurrence of the adverse event and will generate feedback to the principal investigator on strategies to prevent these from occurring if they are preventable events.

6. Issue a report of your adverse event evaluation.

Appendix 6: Serious adverse event reporting format

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Comité de Ética en Investigación Biomédica

FORMULARIO DE EVENTOS ADVERSOS SERIOS EN LA FUNDACIÓN VALLE DEL LILI

Fecha de notificación al CEI:		Fecha de detección del evento:	

Tipo de reporte:	Inicial		Seguimiento #		Final		Reporte inicial fuera de tiempo:	Si		No	

NOMBRE DEL PROTOCOLO:	NÚMERO DEL PROTOCOLO:

ID. del sujeto participante	Edad	Nombre del evento adverso serio (escribir el diagnóstico/signo/síntoma que define el evento adverso)

Fecha de la inclusión						Fecha inicial del evento adverso						Fecha final del evento adverso					
año		mes		día		año		mes		día		año		mes		día	

DESCRIBA EL EVENTO

MEDIO POR EL CUAL SE CONOCIÓ DEL EVENTO ADVERSO

- ☐ Llamada al sujeto o familiar
- ☐ Visita no programada
- ☐ Visita programada / contacto telefónico programado
- ☐ Hospitalización del paciente / interconsulta
- ☐ Revisión de la historia clínica por personal del sitio
- ☐ Revisión de la historia clínica por personal del patrocinador
- ☐ Llamada por parte del personal del sitio (confirmación de visitas)
- ☐ Otra. Explique: _____

Criterio de seriedad: seleccionar de la lista el criterio por el que se determina la seriedad del evento adverso:

- ☐ Resulta en fallecimiento
- ☐ Requiere hospitalización del paciente o prolongación de la hospitalización existente
- ☐ Da como resultado incapacidad/invalidez persistente o significativa
- ☐ Amenaza la vida
- ☐ Es una anomalía congénita/defecto de nacimiento

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Causalidad determinada por el investigador Relación entre la administración del medicamento y la aparición de una reacción adversa						¿El evento está asociado a una desviación al protocolo?			
Probable		Improbable		Relacionada		No relacionada		Si		No	

Clasificación según antecedente estrocinador Esperado ☐ No esperado ☐

Acción emprendida con la medicación o intervención en estudio					
Continúa con la intervención	☐	Suspendida transitoriamente	☐	Ninguna	☐
Suspendida definitivamente	☐	Concluió tratamiento/actualmente sin intervención			☐

DESCRIBA LA S MEDIDA S TOMADA S PARA EL MANEJO DEL EVENTO ADVERSO

SITUACIÓN DEL EVENTO AL MOMENTO DE ESTE REPORTE							
Recupera sin secuelas	☐	Recupera con secuelas	☐	Continúa	☐	Muerte	☐

Si el reporte inicial del evento adverso serio se realiza por fuera del tiempo establecido, diligencie los siguientes campos:

CAUSA S DEL REPORTE DEL EVENTO ADVERSO SERIO POR FUERA DEL TIEMPO

ACCIONE S A REALIZAR PARA EVITAR REPORTAR POR FUERA DEL TIEMPO

Nombre y firma del investigador

MAYO / 2018 – V2. FORMA-1483

Appendix 7: Informed consent

Appendix 8: Declaration of householder.

Appendix 9: Telephone contact follow-up visit day 42 format.

Institution:
Randomization number:
Telephone contact date:

Before to call the patient, please confirm whether the patient received vascular intervention to control intraoperative bleeding: Yes ____ No ____

My name is: _____ I am calling you from the Fundación Valle del Lili from the area of the Clinical Research Center regarding the study in which you agreed to participate.

Today is her 42nd day after the surgery through which she had her baby and we want to follow up on her current health status.

Miss _____ please answer the next questions:

Question	Answer
¿How are you? ¿How do you feel today?	
Have you had any problems or difficulties that required medical attention or consultation since your outpatient appointment?	
In case the patient has consulted a health service, ask where she went and why, and request a copy of the care history if possible. Send all the information to the principal investigator's institutional e-mail address.	
Regarding the wound from your surgery, have you had any problems with it? Exemplify: Is it red, warm, leaking pus or any fluid, confirm that your stitches have been removed.	
* If you have not received vascular intervention, do not ask the following	

question: Since your last outpatient follow-up appointment, have you had tingling or numbness in your legs, skin changes such as bluish, purple or red coloration, swelling or pain?	

Very thanks Miss _____ with this call we would like to end your participation in the study, we thank you very much for your commitment, we hope you continue very well, see you soon.

Appendix 10: standardized surgical techniques and intra-operative imaging manual

Technical conditions for intraoperative imaging:

1. The taking of photos and videos will be performed by the sub-investigator or delegated to a member of the surgical team in case the sub-investigator is not available.
2. The photo taker will use all necessary biosafety items to enter the surgical field.
3. The taking of photos and videos may be done by means of a mobile device camera or a standard or professional camera.
4. The taking of photos and videos will be done in a medium, short or detailed photographic plane according to the photographic moment to be captured.
5. The photos of the resected macroscopic piece (uterus, uterine segment or placenta) will be taken on a clean background to improve its visualization.
6. The format of captured images should be JPEG and the video format should be MP4.
7. The maximum duration of each video will be 30 seconds.

Description of the surgical technique:
Asepsis and antisepsis of skin and vagina 2.
Skin incision: Vertical or horizontal.

3. Fascia incision: Vertical or horizontal
4. Dissection by planes up to the abdominal cavity
5. Identification of findings: (Take photo presence or absence of PAD).
6. Intraoperative staging:
    a. Opening of the right parametrium: (Take photo)
    b. Left parametrial opening: (Take photo)
    c. Retrovesical dissection: (Take photo)
    d. Vesicouterine bypass: description of the findings (fibrosis?)
7. Hysterotomy:
8. Management of placenta previa or placenta previa: Ward's maneuver.
9. Fetal extraction: time, presentation, weight, length, APGAR, amniotic fluid characteristics.
    a. Clamping, cutting and ligation of the umbilical cord.
    b. Delivery: Does spontaneous delivery occur? Yes/No
10. Hysterotomy management: Hysterorrhaphy or hemostasis with forceps?
11. Vesicouterine dissection is completed
12. Partial myometrial resection vs. total or subtotal hysterectomy.
    a. Partial myometrial resection:
        i. Hemostatic sutures obliterating colpouterine pedicles.
        ii. Resection of abnormal myometrium (segmentectomy) with attached placenta (Take photo).
        iii. Complete placental delivery
        iv. Control of bleeding placental insertion bed (if applicable).
        v. Uterine reconstruction with two layers of suture, the first with "U" stitches and the second with invaginating uninterrupted suture (Take photo).
        vi. Revision of hemostasis of the anterior face of the uterus and

posterior face of the bladder.
vii. Describe if uterine compressive sutures are required.

b. Hysterectomy
i. Sequential clamping, cutting and ligation of round ligaments, ovarian uterus, uterine arteries, uterosacral ligaments and vaginal vault.
ii. Vaginal vault is fixed with uterosacral ligaments.
iii. Review of hemostasis bases of parametrium and posterior aspect of bladder.
iv. Take a photo of the extracted surgical specimen.

13. Counting of complete compresses
14. Closure of the abdominal wall in planes
a. Fascia with ___
b. Skin with ____

Photos list

Partial myometrial resection	Hysterectomy
1.Step 5: Identifyng of surgical findigns	1.Step 5: Identifyng of surgical findigns
2.Step 6: A. Right parametrial opening	2.Step 6: A. Right parametrial opening
3.Step 6: B. Left parametrial opening	3.Step 6: B. Left parametrial opening
4.Step 6: C. Retrovesical dissection (Pelosi)	4.Step 6: C. Retrovesical dissection (Pelosi)
5.Step 12: A.II. Resection of abnormal myometrium (segmentectomy) with attached placenta	5.Step 12: B.V. extracted surgical specimen
5.Step 12: A.V. Uterine reconstruction with two layers of suture	

Appendix 11: Standard surgical note

Surgical informed consent

1. Asepsis and antisepsis of skin and vagina.
2. Skin incision:
3. Incision in fascia:
4. Dissection by planes up to the abdominal cavity
5. Identification of findings:
6. Intraoperative staging:
    a. Right parametrial opening:
    b. Left parametrial opening:
    c. Retrovesical dissection - Pelosi maneuver:
    d. Vesicouterine bypass:
7. Hysterotomy:
8. Management of placenta previa:
9. Fetal extraction: time, presentation, weight, length, APGAR and amniotic fluid characteristics.
    a. Clamping, cutting and ligation of the umbilical cord.
    b. Delivery: spontaneous delivery occurs:
10. Hysterotomy management: hysterorrhaphy or hemostasis with forceps: 11.
11. Vesicouterine dissection is completed
12. Myometrial partial resection vs. total or subtotal hysterectomy
    a. Partial myometrial resection:
        i. hemostatic sutures obliterating colpouterine pedicles
        ii. Resection of abnormal myometrium (segmentectomy) with attached placenta.
        iii. Complete placental delivery
        iv. Control of bleeding placental insertion bed (if applicable).
        v. Uterine reconstruction with two layers of suture, the first with "U" stitches and the second with invaginating uninterrupted suture.
        vi. Revision of hemostasis of the anterior face of the uterus and posterior face of the bladder.
        vii. Describe if uterine compressive sutures are required.

    b. Hysterectomy
        i. Sequential clamping, cutting and ligation of round ligaments, ovarian uterus, uterine arteries, uterosacral ligaments and vaginal vault.
        ii. Vaginal vault is fixed with uterosacral ligaments.
        iii. Review of hemostasis bases of parametrium and posterior aspect of bladder.
        iv. Take a photo of the extracted surgical specimen.

13. Counting of complete compresses
14. Closure of the abdominal wall in planes
    a. Fascia with PDS
    b. Skin with prolene

Complications:
1. Cystotomy:
2. Ureteral injury:
3. Other:

The following variables of interest for the study are verified:

Screening failure: YES / NO
Gestational age at birth: SS

Time of start of procedure (Skin incision): 00h:00min (24h format)
Time of end of procedure (Skin closure): 00h:00min (24h format)
Type of anesthesia used in the procedure: .....
Type of skin incision: .....
Type of uterine incision: .....
Use of vascular interventions: YES / NO.
Use of Cell saver: YES / NO
Status of the newborn: Alive / Dead
Weight: grams.

Estimated bleeding by count and weight of soaked pads: 0000cc.
Estimated bleeding by calibrated vaginal collection bag: 00cc
Estimated bleeding by suction devices: 0000cc
Total intraoperative bleeding: 0000cc

FIGO classification for PAS: Grade.....
Topographic classification of PAS: .....
Classification according to Palacios Jaraquemada: Type.....

Blood component transfusion: YES / NO
Administration of lyophilized fibrinogen: YES / NO
Uterine tamponade with hydrostatic balloons: YES / NO
Bladder injury: YES / NO
Ureteral injury: YES / NO
Intestinal injury: YES / NO

Intraoperative bleeding:
1. Quantified bleeding when weighing the compresses:
2. Quantified bleeding on suction devices:
Quantified bleeding in pelvic collecting bag:

Use of cell saver:

Transfusion during surgery:

Recording of operative time.
Time of onset of anesthesia:

2. Time of start of surgery (Skin incision):
3. Time of birth:
4. Time of completion of surgery (Skin Closure):

Type of Anesthesia used in the surgical procedure:

Vascular Interventions:

Clinical Diagnosis:
1. Presence of PAS:
2. FIGO Classification:
3. Topographic classification:
4. Palacios Jaraquemada Classification: