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The Clinical Profile of the Woman at Increased Risk of Placenta Accreta Spectrum Disorders: a Systematic-Review and Meta-Analysis

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The Clinical Profile of the Woman at Increased Risk of Placenta Accreta Spectrum Disorders: a Systematic Review and Meta-Analysis

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Abbreviations

ACOG	American College of Obstetricians and Gynecologists
AFP	Alpha-fetoprotein
AP	Acretismo Placentário
ART	Assisted Reproductive Techniques
BMI	Body Mass Index
CI	Confidence Intervals
CS	Cesarean section
DC	Dilation and Curettage
DIC	Disseminated Intravascular Coagulopathy
EW-AIP	European Working Group on Abnormal Invasive Placenta
FIGO	International Federation of Gynecology and Obstetrics
HCG	Human Chorionic Gonadotropin
IVF	In vitro Fertilization
MRI	Magnetic Resonance Imaging
OR	Odds Ratio
PAPP-A	Pregnancy-Associated Plasma Protein A
PAS	Placenta Accreta Spectrum
PICO	Population, Intervention/Exposure, Comparison, Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
SGO	Society of Gynecologic Oncology
SMFM	American Society for Maternal-Fetal Medicine
VBAC	Vaginal Birth After Cesarean

Abstract

Background Although still infrequent, PAS disorders remain one of the most important causes of maternal mortality and morbidity in modern obstetrics. They represent a potentially life-threatening event, especially if not detected before delivery, as they may cause massive obstetric hemorrhage and related complications, such as the need for several blood transfusions, hemorrhagic shock, disseminated intravascular coagulopathy, sepsis, and multiorgan failure. It often ultimately needs an emergency hysterectomy to prevent maternal death. Prenatal diagnosis is key because it provides an opportunity to optimize management and outcomes. Moreover, its contemporary global trend highlights the clinical need for an effective systematic screening guideline for this disorder in referring healthcare settings. The combination of prenatal imaging with maternal and pregnancy risk factors has been reported to improve the predictive accuracy of the presence and severity of PAS.

Objectives To perform a systematic review and meta-analysis of the possible major clinical risk factors for PAS and estimate risk. The primary goal is to establish the clinical profile of the woman at increased risk, combining the clinical risk factors associated with PAS into a practical screening guideline. With these data, we can identify the women that will benefit from an early referral to experts, which may increase the rate of antenatal diagnosis and reduce PAS-related complications with proper planning and follow-up.

Methods This systematic review and meta-analysis were conducted following the PRISMA checklist and flowchart. A literature search was performed in three databases - PubMed, EMBASE, and The Cochrane Library -, between June 2022 and December 2022. The study protocol was registered in PROSPERO with the registration ID CRD42023360340. The research question was defined using PICO principles. Initial decisions to include or exclude studies were focused on the study title, and subsequent decisions were then centered on the abstract and full body text. With the extracted data, a meta-analysis was performed when possible. To assess heterogeneity between studies, Cochran's Q test and the I^2 index were used.

Results A total of 36 studies were finally included in the systematic review. We found that placenta previa (OR 34.69, 95%CI[9.41; 127.89]), a history of two or more previous cesarean sections (OR 5.84, 95%CI[2.69; 12.67]), assisted reproductive technology (OR 4.19, 95%CI[3.06; 5.73]), uterine interventions (OR 3.41, 95%CI[2.37; 4.92]), and multiparity (OR 3.22, 95%CI[1.26; 8.24]) are all risk factors for the development of PAS disorders. Women with placenta previa had the highest risk. Results regarding maternal BMI and smoking during pregnancy were not statistically significant.

Conclusions Safe and effective care of a woman with a PAS disorder depends on timely diagnosis. Our results directly impact the ability of screening and, thus, improve the management of women at high risk for this potentially life-threatening condition.

KEYWORDS: Placenta Accreta Spectrum; Abnormal Placentation; Prenatal Diagnosis; Early Screening; Clinical Risk Factors.

Resumo

Antecedentes Embora raro, o Acretismo Placentário destaca-se como uma das causas mais importantes de mortalidade e morbilidade maternas na obstetrícia moderna. É potencialmente fatal, especialmente se não for diagnosticado antes do parto, pois pode ser causa de hemorragia obstétrica maciça, e complicar-se com a necessidade de múltiplas transfusões sanguíneas, choque hemorrágico, coagulopatia intravascular disseminada, sépsis e falência multiorgânica. Adicionalmente, muitas vezes a sua abordagem implica uma histerectomia de emergência, necessária para evitar a morte materna. O diagnóstico pré-natal é fundamental pois proporciona uma oportunidade para otimizar a sua abordagem, minimizando assim os riscos e complicações associados. A tendência global para o aumento da incidência do AP realça a necessidade clínica de uma orientação para o seu rastreio sistemático eficaz. A combinação das técnicas de imagem pré-natais com os fatores de risco maternos tem sido descrita como promissora na melhoria da precisão preditiva de ambas a presença e gravidade desta patologia.

Objetivos Realizar uma revisão sistemática e meta-análise dos possíveis fatores de risco clínicos associados com o desenvolvimento de AP e estimar os riscos individuais. O principal objectivo é estabelecer o perfil clínico da mulher com risco aumentado, combinando os fatores de risco encontrados numa diretriz prática de rastreio e diagnóstico que possa ser facilmente implementada. Assim, tentaremos identificar as mulheres que beneficiam de uma referenciação precoce a cuidados de saúde especializados, o que pode aumentar a taxa de diagnóstico pré-natal e reduzir as complicações, ao permitir o planeamento e acompanhamento adequados.

Métodos Esta revisão sistemática e meta-análise seguiu os itens da check-list e do fluxograma do PRISMA. A pesquisa bibliográfica foi realizada em três bases de dados - PubMed, EMBASE e The Cochrane Library-, entre Junho de 2022 e Dezembro de 2022. O protocolo de estudo foi registado no PROSPERO com o ID CRD42023360340. A pergunta de investigação foi definida utilizando os princípios PICO. As decisões iniciais de inclusão e exclusão de artigos basearam-se no título do estudo e as decisões subsequentes no resumo e corpo de texto. Com os dados extraídos, foi realizada uma meta-análise sempre que possível. Para avaliar a heterogeneidade entre estudos, foram utilizados o teste Q de Cochran e o índice I^2.

Resultados Um total de 36 estudos foram incluídos na revisão sistemática. Verificámos que a placenta prévia (OR 34,69, IC95%:[9,41; 127,89]), história obstétrica de duas ou mais cesarianas (OR 5,84, IC95%[2,69; 12,67]), o uso de técnicas de reprodução assistida (OR

4.19, IC95%[3,06; 5,73]), antecedentes de intervenção uterina (OR 3,41, IC95%[2,37; 4,92]), e multiparidade (OR 3,22, IC95%[1,26, 8,24]) são fatores de risco para o desenvolvimento de AP. Os resultados da associação com o IMC materno e tabagismo durante a gravidez não foram estatisticamente significativos.

Conclusões O tratamento seguro e eficaz de uma gravidez complicada com Acretismo Placentário depende de um diagnóstico atempado. Os nossos resultados impactam diretamente o rastreio individual e, assim, melhoram a gestão das mulheres com perfil clínico de alto risco para esta patologia potencialmente ameaçadora da vida.

PALAVRAS-CHAVE: Acretismo Placentário; Anomalias da Placentação; Diagnóstico pré-natal; Rastreio Precoce; Fatores de Risco Clínicos;

Introduction

The placenta is an essential and unique vital organ that develops within the uterine cavity during pregnancy, connecting the mother and the fetus. It is the meeting point between fetal and maternal circulation, supporting fetal growth *in utero* - it has key functions in both respiratory and metabolite exchange, providing nutrition and oxygen to the fetus and removing waste material and carbon dioxide -, as well as in hormone synthesis and regulation.[1]

This endocrine function affects pregnancy, metabolism, fetal growth, and parturition. The placenta also protects the fetus from infections and other maternal disturbances, while helping in the development of the fetal immune system. It grows and matures throughout pregnancy, normally detaching from the uterus after delivery.

Placenta Accreta Spectrum (PAS) is a relatively new umbrella term implemented with the 2019 FIGO consensus guidelines[2], and approved by SGO, ACOG, and SMFM, used for describing a complex disorder of placental development. It was initially described in 1937, in the US, by Irving and Hertig as “morbidly adherent placenta” and it has since been redefined, as it is now known that it encompasses both abnormal adherence and abnormal invasion. There are three grades of PAS[2], that depend on the depth and severity of myometrial invasion: in *accreta*, rather than being restricted within the decidua basalis, the chorionic villi attach to the myometrium; in *increta*, the chorionic villi invade into the myometrium; in *percreta*, this invasion goes through the perimetrium, to and beyond the uterine serosa.

The most consensual explanation regarding its etiology hypothesizes that a defect of the endometrial-myometrial interface leads to an abnormal decidualization in an area of scar tissue, which allows abnormally deep placental anchoring villi and trophoblastic infiltration. [2]

Its clinical relevance relies mainly on the fact that this abnormal adherence and/or invasion affects the normal detachment of the placenta during labor, leading to significant maternal mortality and morbidity.[2,3] Massive obstetric hemorrhage is one of its major complications, possibly leading to hemorrhagic shock, coagulopathy, and injury to surrounding organs, particularly the urinary tract system, often needing a peripartum hysterectomy to prevent maternal death. [2,4–6]

Understandably, it can also have a tremendous psychological impact - women with PAS face increased risks of fertility loss, prolonged hospital admission, and overall morbidity.[7] These are all important stressors that increase the risk for perinatal mental health disorders, a period in a woman’s life already more intrinsically vulnerable to these conditions.

Although infrequent, it represents a growing obstetric concern – the increasing rate of PAS worldwide projects that by 2025, 1 in 200 women undergoing a cesarean delivery will have a

diagnosis of PAS, with a mortality rate as high as 7% and even higher in under-developed nations. [8]

In PAS, maternal mortality and morbidity are significantly reduced when the delivery occurs in a specialized center, by a multidisciplinary care team experienced in managing the surgical and perioperative challenges presented by these disorders.[9] A planned delivery with a multidisciplinary approach is associated with shorter operative time, decreased maternal hemorrhagic morbidity, and fewer intensive care unit admissions, as well as better neonatal outcomes. [10,11]

In 2015, the American College of Obstetricians and Gynecologists (ACOG) and the American Society for Maternal-Fetal Medicine (SMFM) developed a standardized risk-appropriate care system for facilities, based on region and expertise of the medical staff, designated as “levels of maternal care” [12], to reduce overall maternal morbidity and mortality in the United States, that stated that PAS patients should receive a level III – subspecialty - or higher care. [13]

This multidisciplinary team consists of experienced obstetricians, gynecologists, obstetric anesthesiologists, urologists, interventional radiologists, neonatologists, and reliable access to interdisciplinary staff with expertise in critical care, including nurses skilled in managing high-level postpartum hemorrhage and access to a blood blank capable of employing massive transfusion protocols. [2,5]

In 2018, the International Federation of Gynecology and Obstetrics (FIGO) Obstetric Care Consensus on PAS[4] determined that its diagnosis should be determined by diagnostic imaging and histopathology results combined with the clinical information.

Imaging modalities are known to play a crucial role. Obstetric ultrasonography is used as the primary diagnostic modality for antenatal diagnosis, given that it is non-invasive and that the signals associated with PAS disorders may manifest as early as the first trimester, making it an essential tool for early detection and management of this condition. [4] Still, the majority of diagnosis is made during the second or third trimesters. Magnetic resonance imaging (MRI), on the other hand, is not the preferred recommended modality for the initial evaluation of a suspected PAS, as it is still unclear whether it improves diagnosis beyond what is achieved with an ultrasound.[2] Studies show that it may be useful in some, more difficult cases, such as posterior placenta previa and to assess disease extent and depth of invasion in a suspected percreta. [3,14]

Furthermore, the evaluation of a suspected PAS via any imaging mode brings a few problems [4,8,15,16]: (1) although there is a standardized description and reporting guidelines for ultrasonography findings of PAS, these are not yet in widespread use globally, (2) it is always

subjective, depending largely on the experience of the operators, explaining why there is a significant interobserver variation in the interpretation of findings (3) so far, the prenatal diagnosis of PAS has not been included in standardized training as screening for maternal-fetal structure malformations, (4) it is affected by the patient's body constitution/phenotype and (5) the absence of ultrasound abnormal findings does not exclude a diagnosis of PAS.

In the efforts to reduce these limitations, more research has been made on this topic and some measures have been implemented in the last decade[8]: to reduce inter-operator variability, in 2016 the European Working Group on Abnormal Invasive Placenta (EW-AIP) proposed the ultrasound descriptors that should be used for diagnosis; in 2022, Giuseppe Calli *et al.* [17] reported that the predictive accuracy of ultrasound signs can be enhanced by combining various clinical risk factors - such as previous cesarian delivery, parity, and previous abortion –, with higher sensitivity, specificity, positive and negative predictive values; Mittal P *et al.* [18] also noted that the diagnosis' sensitivity of ultrasound was notably lower when the operators were blinded to the woman's clinical history.

Regarding histopathological analysis, current PAS pathology terminology and diagnostic criteria separate the nomenclature for hysterectomy specimens from that for delivered placentas, allowing more clear and more consistent communication among healthcare providers.[20]. Moreover, in PAS a confirmation of the diagnosis is only obtained if a hysterectomy or partial myometrial resection is performed[21], which is not always the case.

As recent studies have shown[15,17,22,23], adding clinical information improved the predictive accuracy of the diagnosis and severity of PAS. While it is understood that abnormal results of placental biomarkers - such as pregnancy-associated plasma protein A (PAPP-A), alpha-fetoprotein (AFP), and human chorionic gonadotropin (HCG) - are linked to an increased risk of PAS, they are too nonspecific for clinical use.[4] Thus, clinical risk factors remain particularly important as predictors of this condition.

It is also very important to note that in PAS, the referral of suspected cases has been suggested as the most important measure in determining both maternal and neonatal outcomes, as the work of Schwickert *et al.* [24,25] noted, thus implying that it is possible to optimize outcomes, even among women with a clinical high-risk profile.

This referral, however, relies on both identification of the women at risk and accurate prenatal diagnosis. Still, recent population studies have shown that PAS disorders remain undiagnosed until delivery from half to two-thirds of the cases.[3] Typically, such cases are identified during labor when the placenta is retained, and/or there is hemorrhaging while attempting to remove it manually. [26]

The major factors that increase the risk of developing PAS are widely recognized, and the majority of cases is associated with placenta previa and a history of cesarean delivery. Furthermore, the likelihood of developing PAS increases with each successive cesarean delivery.[27] Other risk factors have also been identified, such as maternal age, multiparity, uterine interventions, and assisted reproductive techniques (ART). [2]

Ultimately, it appears evident that a more comprehensive understanding of the clinical profile of women who are at a higher risk of developing PAS disorders would represent a significant advancement in guiding targeted prenatal screening efforts and increasing the rate of antenatal diagnoses.

Methods

Study Design

The present systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist.

The study protocol was registered in PROSPERO with the registration ID CRD42023360340.

The research question was defined using the Population, Intervention/Exposure, Comparison, and Outcome (PICO) principles. The population was the general obstetric population. The intervention/exposures were the following maternal clinical risk factors: number of previous cesarian deliveries, presence of placenta previa, maternal age, gravidity and parity, maternal BMI, previous uterine intervention, assisted reproductive techniques (ART), and a history of smoking during pregnancy. The comparator was the absence of the previously named risk factors. The main outcome was the occurrence of PAS.

Placenta Accreta Spectrum was defined as the range of pathologic adherence of the placenta, including placentas increta, percreta, and accreta. We included both the cases where a histopathologic confirmation was obtained, if a hysterectomy was performed, and the clinically diagnosed cases of PAS – categorized into "clinical PAS" -, when a conservative approach was taken.

The manifestations of **"clinical PAS"** included at least one of the following: (1) the absence of placenta separation 30 minutes after vaginal delivery, despite active management in third-stage labor, including intravenous infusion of synthetic oxytocin, uterine massage, and controlled cord traction, (2) difficult manual or fragmentary removal of the placenta and heavy bleeding from the placentation site, with partial or no placental separation during delivery and (3) evidence of gross placental invasion intraoperatively.

Placenta previa was defined as the implantation of the placenta over or very near (<2 cm on ultrasound) to the internal cervical OS.

The number of **previous cesarian deliveries** was considered as 2 or more.

Maternal age was divided into three categories: younger than 25 years; between 25-34 years old; and 35 years old or older, which was considered advanced maternal age.

Parity was divided into two groups: nullipara (no previous delivery ≥28 weeks of gestation) and multipara.

Maternal BMI was categorized into 4 groups, according to the classification of the World Health Organization: underweight (BMI<18.5 kg/m^2); normal weight (BMI=18.5–24.9 kg/m^2); overweight (BMI= 25.0-29.9 kg/m^2) and obese (BMI= ≥30 kg/m^2).

Uterine interventions included history of previous uterine surgery, dilation and curettage, and manual removal of the placenta.

The **ART** considered included in vitro fertilization (IVF), gamete intrafallopian tube transfer (GIFT), intracytoplasmic sperm injection (ICSI), and intrauterine insemination (IUI).

Search Strategy

The search was conducted in three databases, containing multidisciplinary and health science publications - PubMed, EMBASE, and The Cochrane Library.

Systematic search strategies were used applying filters by language, year of publication, and type of study. Search terms were as follows: (1) [(placenta increta) OR (placenta percreta) OR (placenta accreta) AND (risk factors)], for PubMed; and (2) [(placenta accreta spectrum) AND (clinical risk factors)], for both EMBASE and The Cochrane Library.

The detailed search strategy is presented in **Supplementary Material I (SI)** and includes the combination of relevant medical subject heading (MeSH) terms, synonyms, and keywords used.

Eligibility Criteria

Studies that fulfilled the following inclusion criteria were included (1) articles focused on the clinical risk factors associated with the Placenta Accreta Spectrum, confirmed clinically and/or histopathologically, in the general obstetric population, (2) studies that were published in 2019 and beyond, after the 2019 FIGO's Clinical Grading System was established (3) studies limited to the English and Portuguese languages (4) studies limited to human subjects.

Articles were excluded if any of the following applied: (1) incomplete data or information, (2) related only to risk factors that were not clinical, (3) related exclusively to the management or treatment of PAS, rather than its diagnosis, (4) focused only on the prenatal imaging techniques of diagnosis, (5) designed as a case report or case series, and (6) animal studies and genetic studies.

Data extraction and Study Selection

Extracted information was stored on Microsoft Excel spreadsheets. First, the articles were checked for duplicates by A.S. The remaining articles were then independently screened for inclusion criteria by two reviewers (A.S and M.S), based on titles and abstracts. The reasons for excluding trials were recorded. If there was a disagreement, the opinion of M.S. prevailed.

Next, a screening of the full-text reports of the remaining articles was performed, after which it was decided whether those met the inclusion criteria.

Then, the found eligible articles were carefully analyzed and the following information was extracted: study characteristics (first author, publication year, study design, country, sample size) participant characteristics (population demographics and risk factors), and p-values, the measure used for the point estimates (odds ratio/ related risk/ hazard ratio) and all the other relevant data possibly needed for doing the analysis.

Synthesis of Results and Meta-Analysis

With the extracted data, a meta-analysis was performed when possible.

Articles reporting the incidence of PAS, regardless of the population studied, were chosen to perform a meta-analysis on incidence. Articles that contained information on the studied clinical risk factors able to be used in a meta-analysis were also included.

To perform the meta-analysis, we used a random effects model, which is a more conservative approach and is generally more appropriate for dealing with heterogeneity among the included studies. This model takes into account both sampling error and actual variation in effect estimates across studies and can provide a more accurate and reliable estimate of the aggregate effect.

To assess heterogeneity between studies, Cochran's Q test and the I^2 index were used. Cochran's Q test is a statistical measure that assesses heterogeneity between studies, based on the differences between observed and expected outcomes. The I^2 index, in turn, is a measure of heterogeneity that expresses the proportion of the total variability observed among studies that is due to heterogeneity, rather than sampling error. I^2 values above 50% are usually considered indicative of substantial heterogeneity.

To evaluate different clinical risk factors for PAS, we conducted meta-analysis that considered the values reported in different articles that had PAS as a dependent variable. The risk was assessed by odds ratio, and whenever a minimum of two articles reported an odds-ratio value corresponding to the risk factor in question, the aggregate odds ratio was calculated

using a random effects model. In some cases, the authors did not report the odds ratio but included values that allowed its calculation, so this information was also included.

The results of the meta-analysis are presented in forest plots, that provide a visual overview of the effect estimates from each study included, as well as the overall pooled effect estimate and its confidence intervals.

The analysis was performed in R using the package metafor, and a significance level of 0.05 was considered. Forest plots were produced in MS® Excel® from the R results.

Quality Assessment and Risk of Bias

Quality assessment of the included studies was conducted as explained below:

(1) Quality Assessment for the included Systematic Reviews and Meta-analysis was performed following an adapted version of the “Quality Assessment of Systematic Reviews and Meta-Analysis tool by the American National Heart, Lung and Blood Institute (NHLBI)”;

(2) Quality Assessment for the included Review Articles was conducted following the “Scale for the Assessment of Narrative Review Articles (SANRA)”;

(3) Quality Assessment for the included Observational Studies and Original Articles was performed following an adapted version of the “Quality Assessment of Observational Studies tool by the American National Heart, Lung, and Blood Institute (NHLBI).

The complete detailed Quality Assessment can be found in **Supplementary Material II (SII).**

Results

Study Characteristics

The systematic literature search identified a total of 844 articles, using the MeSH keywords on the three databases previously mentioned – 643 from PubMed, 195 from Embase, and 6 from Cochrane Central Register of Controlled Trials.

A total of 465 studies were removed before the screening process, because they were not in the English language or were published before 2019, given that the focus was to be on studies published after the 2019 FIGO's Clinical Grading System was established, to support the process of clarifying reported data on PAS in international literature.

The remaining 379 articles were then screened by title and abstract, after which 276 were excluded. A total of 103 articles were deemed eligible for full-text review and as a result, **36** studies were included in the final stage. The PRISMA flow diagram for the identification of studies is presented in **Figure 1.**

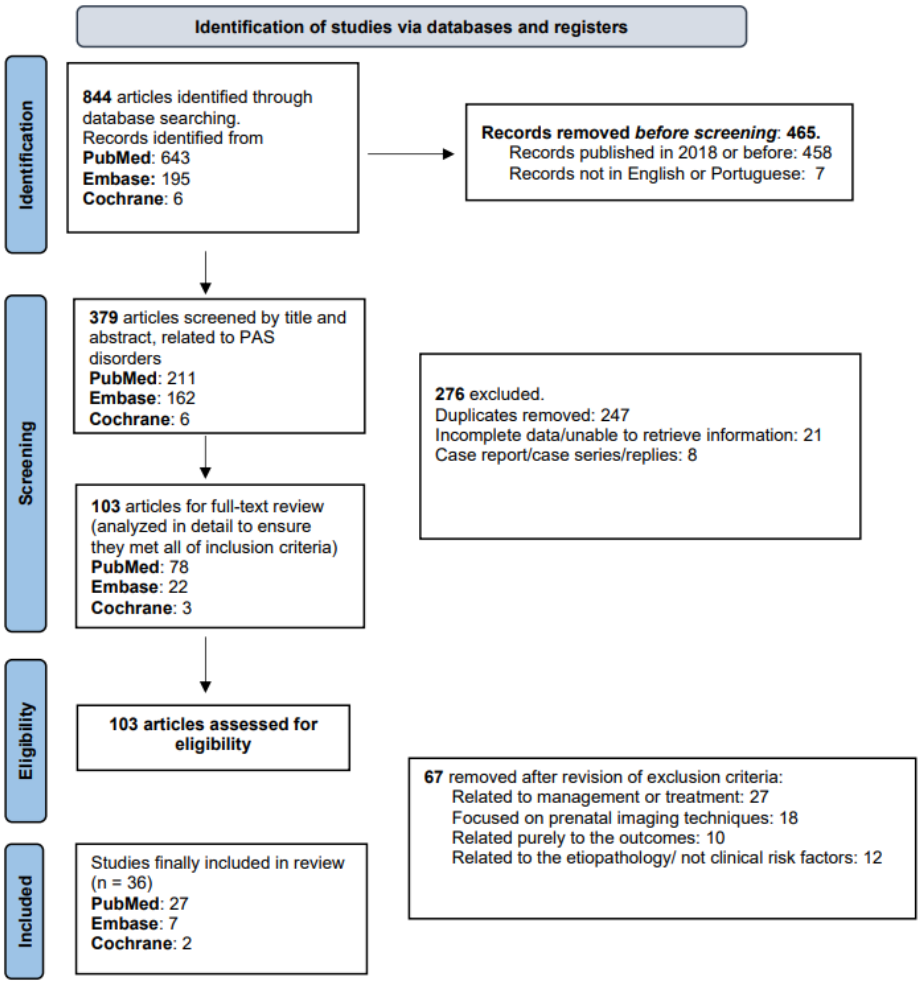

Figure 1 – PRISMA flow diagram of the identification of screened and included studies.

Characteristics of the included studies are summarized in **Table 1**, presented below. Of the 36 studies, the majority were conducted in China and the USA, followed by Italy.

From the 36 articles included in the systematic review, only the ones that contained valid values to be used in the meta-analyses were considered to compute the corresponding pooled summary measures. In "maternal age", "number of fetuses/multiple gestations" and "hypertension disorders", it was not possible to find sufficient information, so these risk factors were not included in the meta-analysis.

Only the forest plots for the studied clinical risk factors that were deemed statistically significant are presented below. However, all the forest plots obtained are included in **Supplementary Material III (SIII).**

STUDY CHARACTERISTICS

FIRST AUTHOR, YEAR, COUNTRY	STUDY DESIGN	POPULATION	SAMPLE SIZE AND SELECTION	STATISTICAL ANALYSIS	MAIN CONCLUSIONS
Yanhong Ming, 2022, China	**Observational cross-sectional survey**	75 132 births, chinese pregnant women	• used data from the China Labor and Delivery Survey, from 96 hospitals in 24 provinces in China between 2015 and 2016. • analyzed the demographic characteristics and prevalence of PAS; • calculated and compared the prevalence of PASD in different regions of China.	• used multivariable logistic regression to examine the association of previous caesarean section and repeated surgical abortion with PAS; • explored the association of PASD with severe adverse perinatal outcomes, which indicated by Weighted Adverse Outcome Score (WAOS) ≥ 20; • used multivariable logistic regression to examine the association of PASD with WAOS;	• the prevalence of PAS in China was higher than in other countries and varied substantially by geographic regions; • two or more previous CS and repeated surgical abortion were major risk factors for PAS; • pregnant women with PAS had more severe adverse pregnancy outcomes • reducing primary cesarean section and repeated surgical abortion are the key to decreasing PAS;
Ensiyeh Jenabim, 2022	**Umbrella Review**	synthesizes evidence from previously published systematic reviews and meta-analyses	• searched PubMed, Scopus, and Web of Science until October 14, 2021; • included all meta-analyses that focused on assessing the risk factors associated with PAS;	• calculated summary effect estimates, 95% CI, heterogeneity I^2, 95% prediction interval, small-study effects, excess significance biases, and sensitive analysis • the quality was evaluated with A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2;)	• multifetal gestation and IVF were environmental risk factors for PAS; • hypertension disorders, low SES, and male fetus were the protective factors;
Rhiannon Heading, 2022, Australia	**Cohort observational study (retrospective review, single tertiary center)**	all births complicated by PAS between June 2006 and July 2020 (n=134 cases)	• the cohort was selected from a site-specific database of all PAS deliveries; • if more than one subtype of PAS was recorded on the report, the most significant invasion was recorded as the final diagnosis; • collected information on maternal demographics and previous history, including information on previous births, a prior history of uterine surgery and antenatal imaging results; • collected maternal and neonatal outcomes – including antenatal admission, scheduled or unscheduled delivery, type of skin and uterine incision, blood loss, need for hysterectomy, gestation at delivery and birthweight.	• analyzed cases with and without a placenta previa to compare differences in maternal risk factors, outcomes and histological diagnosis; • Fisher's exact test was used to analyse categorical variables, • Student's t-test for paired continuous normally distributed variables • Used Mann– Whitney U test for non-normally distributed continuous variables.	• suspected PAS without placenta previa is at lower risk of hysterectomy and massive blood loss. • antenatal diagnosis can be difficult to accurately predict the degree of invasion, and a higher level of suspicion is required.

Panchan Zheng, 2022, China	**Observational retrospective study**	5527 women recruited, of which 2614 had an abnormal placenta	• patients were recruited from 2010 to 2019, at the International Peace Maternity & Child Health Hospital.	• used logistic regression models to analyze the associations between placental abnormalities and gestational hypertension and preeclampsia • conducted propensity score matching (PSM) to reduce confounders. • three models were used for the analysis of the associations between PIAs and GH-PE – (1) unadjusted, (2) adjusted for age and BMI, and (3) logistic regression model, to analyze the effect while adjusting for potential confounding variables, including maternal age, gravidity, parity, previous CS, and BMI.	• placenta previa, especially when complete, is associated with a lower risk of preeclampsia. • placenta accreta is associated with higher risks of GH-PE.
Julieth López, 2022, Colombia	**Systematic review**	140 articles, including, 55 patients	• reviewed different databases including PubMed, MEDLINE Complete, Scopus, Web of Science, EMBASE, SciELO, LILACS, and Ovid; • included patients with PAS disorders in the first trimester of pregnancy who were reported up to November 2018; • described risk factors, imaging techniques used for diagnosis, and outcomes.	• pregnant women included in the studies had a median age of 34 years, median of 4 previous pregnancies, 2 births, 2 caesarean deliveries and 0 miscarriages.	• PAS disorders in the first trimester mostly occurred in the context of patients with known risk factors and/or miscarriage symptoms.
Giuseppe Cali, 2022; Italy	**Case series and systematic review**	12 twin pregnancies complicated by PAS	• retrospective analysis of all twin pregnancies complicated by PAS from two referral centers for PAS disorders in Italy from 2010 to 2015. • retrieved maternal characteristics, including age, parity, body mass index, prior uterine and prior uterine surgery, ultrasound staging, the severity of invasion at histopathology, pregnancy and surgical outcome, and incidence of surgical complications from the hospital electronic database;		• higher risk of preterm birth, antepartum hemorrhage, intraoperative hemorrhage and the need for emergency intervention in twin pregnancies complicated by PAS when compared to what is reported in singleton gestations in the published literature.
Charlotte L, 2022, USA	**Review article**				• the most significant risk factor for PAS is the combination of a prior caesarean delivery and a placenta previa; • pregnant women should be screened for risk factors for PAS.
Zhirong Guo, 2022, China	**Observational retrospective analysis**	Women who underwent cesarean section	• included women who underwent cesarean section with live births at Peking University First	• used logistic regression models to analyze the associations	• the incidence of PAS was 2.4%;

		with live births at Peking University First Hospital from January 2015 to December 2020 were	Hospital from January 2015 to December 2020 • collected demographic and clinical information through chart review. • compared the clinical characteristics and perioperative outcomes of PAS in multiple and singleton gestation;	between multiple gestation and PAS • adjusted for known risk factors and pregnancy complications; • used both univariable and multivariable logistic regression models to investigate the association between PAS and multiple gestation.	• multiple gestation could be independently associated with an elevated risk of PAS. • the clinical characteristics of PAS in the multiple and singleton gestation groups differed significantly in cesarean delivery history and placenta previa.
Ülkü Ayşe Türker Aras, 2022, Polska	**Research paper**	58,895 patients included	• included women from Bursa Yüksek İhtisas Training and Research Hospital in Turkey, between June 2016 and December 2020; • continued with with 27 primiparous PAS and 54 non-primiparous PAS patients, after applying the exclusion criteria; • defined the primary purpose as evaluating PAS risk factors; the secondary ones were to examine maternal and neonatal characteristics.	• used Logistic Regression to analyze the parameters that are significant in terms of PAS risk factors;	• PAS does not occur only in multiparous patients who have a history of previous cesarean section, it also occurs in primiparous patients
Yisu Gao, 2021, China	**Original Article**	pregnant woman who underwent routine ultrasound examination in the third trimester of pregnancy, from January 2014 to November 2018 (n=398)	• retrieved clinical characteristics and outcomes of the patients • recorded maternal characteristics including maternal age, parity, previous vaginal deliveries, previous curettage, previous CS, history of hypertension and diabetes mellitus, prenatal BMI. • recorded ultrasonographic features including abnormal placental lacunae, subplacental hypervascularity, myometrial thinning, placental bulge, bladder wall interruption, location of placenta, placenta previa;	• used Chi square analysis to compare maternal characteristics and two-dimensional sonographic features between PAS group and Non-PAS group; • applied a multivariate analysis to analyze independent risk factors for PAS and calculate the probability of PAS on univariable analysis. • used ROC curves to evaluate the diagnosis power	• the comprehensive scoring system established in this study can effectively diagnose PAS.
Kohei Ogawa, 2021 , Japan	**Retrospective cross-sectional study (registry-based, multicenter)**	472301 women	• included women with reliable data on placenta previa and PAS, with singleton gestation, delivery gestational age 22 weeks or more, between January 2013 and December 2015;	• conducted a multivariable Poisson regression analysis to assess the risk for PAS, stratified by placenta previa • used multivariable Poisson regression analysis to analyze the risk for subsequent blood	• history of CS was the strongest risk factor for PAS among women with placenta previa • among those without placenta previa, ART was an important predictor, but not cesarean section

			• considered PAS as a primary outcome; • considered maternal age, parity, history of cesarean section, history of miscarriage, and ART as potential exposures;	transfusion and hysterectomy by each exposure	
Teresia Svanvik, 2021, Sweden	**Observational cohort study with**	20000 women who underwent routine mid-pregnancy obstetric ultrasound screening between 2013 and 2017	• collected data from women attending routine mid-pregnancy obstetric ultrasound, between January 2013 and December 2017, at Sahlgrenska University Hospital, the largest tertiary center in Sweden; • defined two cohort: women with a suspected cup-shaped placenta (cohort 1, n = 339) and women diagnosed with placenta previa or PAS (cohort 2, n = 227); • analyzed the two cohort according to detection rate, risk factors, and prevalence; • the reference group consisted of women with singleton pregnancies; • retrieved data on covariates from the medical records from the Swedish Pregnancy Register;	• performed no power calculation; • performed analyses of associations between covariates using logistic regression; • tested interactions between covariates; • all tests were two-sided;	• the existing routine mid-pregnancy obstetric ultrasound screening showed low detection rate for placenta previa and PAS • adding risk factors could improve the detection rate. • IVF was identified as the strongest independent risk factor for placenta previa • risk factors were present for all women with PAS
Hitomi Imafuku,2021, Japan	**Prospective cohort study**	Pregnant women (n=4870)	• enrolled women who received maternal checkup and delivered at ≥22 gestational weeks between January 2010 and December 2019 at Kobe University Hospital; • queried all pregnant women about conception by ART, prior history of CS, dilation and curettage, hysteroscopic surgery, myomectomy, and UAE at the first visit	• compared clinical characteristics and findings between pregnant women with and without PAS. • analyzed the differences between the two groups using the Student's t-test, Fisher's exact test, and chi-square test;	• prior history of CS, D&C, hysteroscopic surgery, UAE, current pregnancy via ART, and the presence of placenta previa in the current pregnancy are high risk for PAS;
Valeria Romeo, 2021, Italy	**Retrospective study**	70 patients with placenta previa	• retrospectively selected 70 patients with placenta previa; • retrieved clinical risk factors from medical records; • evaluated US and MRI images to detect imaging signs suggestive of PAS;	• analyzed diferences between patients with or without PAS by unpaired t test or chi-square test, as appropriate; • univariable analysis was performed to identify CRF, US and MRI signs associated with PAS considering histology as standard of reference	• MRI is the best modality to predict PAS in patients with placenta previa, independently from CRF and/or US finding • proposes the combined assessment of clinical risk factors and US as the first diagnostic level to predict PAS, sparing MRI for selected cases in which US findings are uncertain;

				• performed ROC analysis and calculated AUC • also performed multivariable analysis¸ • performed enfold cross-validation for internal validation;	
Nguyen Manh Thang, 2021, Vietnam	**Observational retrospective cohort study**	Patients with PAS disorders in Vietnam (n=255)	• retrospectively reviewed the medical records of patients admitted to the hospital with a diagnosis of PAS disorders >5; • collected data using a self-developed tool that captured general and obstetric characteristics, treatment modality, clinical outcomes, and other information. • demographic and obstetric characteristics included maternal age, socioeconomic status, time at hospital before surgery, parity, previous cesarean section, history of miscarriages, history of preterm labor, placental location and placenta previa • clinical outcomes included pre- and postoperative hemoglobin, blood transfusion, surgical complications, time at hospital after surgery, gestational age at delivery, birth weight, preterm delivery, Apgar scores at 1 and 5 minutes, and neonatal mortality.	• compared the planned vs emergent delivery groups; • compared continuous variables using a 2-sample Student t test. • compared categorical variables using a x2 test • analyzed the timing of delivery in the planned and emergent delivery groups with a Kaplan-Meier statistics and determined their significance by the log-rank test. • used a multivariable logistic regression model to identify independent risk factors associated with delivery type of placenta accreta disorders;	• planned delivery is strongly associated with a lower need for blood transfusion and better neonatal outcomes compared with emergent delivery • antenatal vaginal bleeding and preterm labor are risk factors for emergent delivery among patients with PAS;
Sara Ornaghi, 2021, Italy	**Prospective cohort study (population-based study)**	372 cases of PAS notified during the study period	• the background population comprised all women who delivered in the participating regions during the study period. • included all women aged 15–50 years and delivering at >22 weeks of gestation with a diagnosis of PAS from September 2014 to August 2016; • covered 49% of national births in six Italian regions; • prospectively reported cases by a trained clinician for each	• identified potential factors associated to PAS by calculating unadjusted relative risks (RR) and 95% CI. • compared dichotomous data using Pearson Chi-square test or Fisher exact test for categorical variables and Mann-Whitney test for continuous variables	• antenatal suspicion of PAS is associated with improved maternal outcomes, including in high-risk women with both placenta previa and prior CS, likely because of their referral to specialized centers for PAS management • the estimated prevalence for PAS was f 0.84 per 1000 • Women with PAS had a median age of 35 years at delivery;

			participating maternity unit by electronic data collection forms; • retrieved data from the National Hospital Discharge, when available; when not available, the background population was estimated in aggregate form from the National Birth register;		
Shinya Matsuzaki, 2021, USA	**Retrospective, observational study (population-based)**	2,727,477 cases who underwent cesarean delivery during the study period, 8030 (0.29%) with the diagnosis of PAS	• queried the National Inpatient Sample that (represents >90% of the United States population) • cohort included women who underwent cesarean delivery from October 2015 to December 2017 and had a diagnosis of PAS • defined the main outcome measures as patient characteristics and surgical outcomes;	• used the generalized estimating equation model for multivariable analysis to assess the independent association between PAS and surgical morbidity • used a parsimonious adjustment model based on the assumption that the incidence of PAS is infrequent. • adjusted for predetermined factors: age, year, race or ethnicity, obesity, CCI, previous CD, gestational age, hospital bed capacity, and teaching status; • performed several sensitivity analyses to assess the robustness of study findings. F	• accreta was the most common diagnosis, followed by percreta and increta • patient characteristics and outcomes differ across the placenta accreta spectrum subtypes, and women with placenta increta and percreta have considerably high surgical morbidity and mortality risks. • the incidence seems to be higher than reported in previous studies.
G Kayem, 2021, France	**Prospective population-based study**	249 women with PAS, from a source population of 520 114 deliveries	• included all 176 maternity hospitals of eight French regions • classified women with PAS into two risk-profile groups, with or without the high-risk combination of placenta previa (or an anterior low-lying placenta) and at least one prior caesarean. • compared and described these two groups were described;	• compared categorical variables with Pearson's chi-square test or Fisher's exact test, and quantitative variables with Student's t test or Wilcoxon's rank-sum test, as appropriate. • performed two sensitivity analysis among the subgroups of women: (1) who had had a caesarean section and (2) whose diagnosis was suspected before delivery.	• more than half the cases of PAS occurred in women without the combination of placenta previa and a prior caesarean delivery, and these women had better maternal and neonatal outcomes. • in the group with both factors, PAS was more often suspected antenatally, it was more often percreta and had more hysterectomies, higher rates of blood product transfusions, maternal complications, preterm births and neonatal intensive care unit admissions.
C.M. Coutinho, 2021, UK	**Retrospective study**	57 179 women underwent routine mid-trimester fetal anatomy assessment (220 placenta previa)	• obtained data between 2009 and 2019, involving two groups: 1. a screening cohort of unselected women attending for routine mid-trimester ultrasound assessment; 2. a diagnostic cohort consisting of women referred to the PAS	• performed comparisons between continuous and categorical variables using the Kruskal–Wallis test and the $\chi 2$ square test or Fisher's exact test, respectively. • carried out a univariate binomial logistic regression analysis to determine which	• multiparity, two or more previous CS and placenta previa were the strongest risk factors for PAS; • when linked to a PAS diagnostic and surgical management service, adoption of such a screening strategy has the potential to significantly reduce the maternal morbidity and mortality associated with this condition.

			diagnostic service with a suspected diagnosis of PAS;	risk factors were associated with PAS in women with placenta previa in the screening cohort	
Hadi Erfani, 2021, USA	**Retrospective observational cohort**	1197 subjects	• included subjects who had two consecutive pregnancies delivered at a single, high-volume quaternary care center between 2012-2019. • all included subjects in this analysis underwent detailed placental pathology with a boarded pediatric pathologist subspecializing in placental pathology;	• adjusted for potential confounders; • used logistic regression to evaluate the predictive power of MIP to discriminate index PAS; • performed comparison against well-recognized clinical risk factors;	• microscopic accreta (MIP) is an independent risk factor for PAS in subsequent pregnancy irrespective of other known risk factors.
Nicole L. Vestal, 2021, USA	**Retrospective observational study**	3895707 women, of which 17615 had ART pregnancies	• queried National Inpatient Sample • included women who underwent cesarean section from2015 to 2018; • defined the exposure allocation as the use of ART; • the main outcome measures were abnormal placentation (placenta previa, placenta accreta spectrum, and vasa previa) and perioperative morbidity;	• used multivariable analysis with binary logistic regression models; • controlled for patient demographics, facility characteristics, and pregnancy factors;	• ART may increase the risk of abnormal placentation, which is associated with increased maternal and potentially neonatal morbidity; • ART was independently associated with increased risk of placenta previa, PAS and vasa previa.
Teodora Kolarova, 2021, USA	**Retrospective observational cohort**		• included all subjects who underwent a cesarean hysterectomy for histologically confirmed PAS at a single academic institution between 2011 and 2020. • reviewed antenatal ultrasound images in a blinded fashion for 8 placental findings; • perinatal and delivery outcomes were abstracted.	• compared subjects with a prior CS to those without prior CS using univariate and bivariate analyses;	• PAS without prior CS is characterized by fewer ultrasound findings making it a challenging diagnosis antenatally; • outcomes for this group of patients tend to be more favorable, possibly due to the lesser degree of placental invasion;
Satya Dutta, 2020, India	**Retrospective cross-sectional study**	10 emergency hysterectomy specimens	• included all l women with the antenatal diagnosis of abnormal placentation diagnosed by ultrasound or pregnant women with a history of placenta previa, multiple pregnancies, history of hypertension, previous history of cesarean section, advanced maternal age, women with a previous antenatal history of	• excluded those with spontaneous separation of placenta intraoperatively or any other associated uterine pathology needing hysterectomy; • performed microscopic evaluation on hematoxylin and eosin-stained sections and made the diagnosis of placenta accreta if there was no decidual	• placentas accreta and increta constituted the major forms of abnormal placentation • multiparous women with placenta previa followed by previous lower segment cesarean section and pre-eclampsia were more at risk of having abnormal placentation; • the mean age of presentation was 30.7 years;

			pre-eclampsia, and preterm labor; • studied patients with peripartum hysterectomies due to abnormal placentation presenting with massive hemorrhage from January 2021 to December 2019; • noted the clinical details and relevant obstetrics and gynecological history from the histology requisition forms;	layer between the placental villi and myometrium;	
Dominique A. Badr, 2020	**Literature review**	133 patients	• conducted a search in the Medline database that included all articles published in English or French between 1949 and 201; • included all articles that reported sufficient information concerning risk factors, clinical presentation, management, or outcome of patients with uterine body PAS (non-previa PAS);	• collected and analyzed 133 cases from 109 case reports, 7 case series and 1 retrospective study;	• previous CD, uterine curettage, uterine surgery, Asherman's syndrome, manual removal of the placenta, endometritis, high parity, maternal age and IVF PAS rate will continue to escalate in parallel with the ever-increasing rate of uterine procedures; • maternal age of 35 or more was an independent risk factor for placenta accreta; • multiparity is highly associated with PAS
Bahram Salmanian,2020, USA	**Retrospective analysis that included a prospective cohort**	37,461 deliveries	• primary outcome variable was placenta accreta spectrum	• performed univariate analysis on potential risk factors for predicting PAS • a multivariate model was designed to best fit the prediction of placenta accreta spectrum adjusted for risk factors such as cesarean delivery, placenta previa, age, and parity. • calculated odds as exponential of beta coefficients from the multivariate regression analysis;	• the incidence of PAS 0.6%; • the independent risk factors for PAS were in IVF pregnancy, history of previous cesarean delivery, and presence of placenta previa; • IVF is an independent risk factor for PAS, although its relative clinical importance compared with that of the presence of placenta previa is low.
Daniela A. Carusi, 2020, USA	**Retrospective observational cohort study**	351 deliveries	• included pathology-confirmed PAS deliveries with hysterectomy from two U.S. referral centers from January 2010–June 2019; • compared maternal, pregnancy, and delivery characteristics among PAS cases with (previa PAS group) and without (nonprevia PAS group) placenta previa.	• used two-tailed tests; • used univariate analyses with chi square or Fisher exact tests (when indicated), and Wilcoxon tests for continuous variables • adjusted for multiple variables, with all analyses adjusted for delivery location. • adjusted the analysis of previa status and morbidity for individual factors that have	• PAS without previa is less likely to be diagnosed antepartum, potentially missing the opportunity for multidisciplinary team management; • despite the absence of placenta previa and less placental invasion, severe maternal morbidity at delivery was not lower. • broader recognition of patients at risk for PAS may improve early

			• evaluated surgical outcomes and a composite of severe maternal morbidities, including blood cell units transfused, reoperation, pulmonary edema, acute kidney injury, thromboembolism, or death; • trained research personnel reviewed patients' records for maternal demographic data and obstetric history, established PAS risk factors (presence of placenta previa at delivery, number of prior CS deliveries, prior uterine surgeries, endometrial ablation, IVF conception), antepartum radiologic identification of PAS, and whether care was coordinated by a multidisciplinary abnormal placentation team;	been previously associated with PAS morbidity; • evaluated demographic and obstetric characteristics that were significantly associated with previa status as confounders in this association;	clinical diagnosis and patient outcomes.
Yi-Ping Hou, 2020, China	**Systematic review and meta-analysis**	11 studies with 2,152,014	• based on English- and Chinese-language articles published from January 2014 to June 2019; • retrieved articles Chinese databases (CNKI, Wanfang Data, China Science and Technology Journal Database, CBM) and English databases (PubMed, Web of Science, the Cochrane Library and Embase);	• performed meta-regression analysis including study-level covariates such as country, study design, published year; • performed quality assessment scores to investigate sources of heterogeneity. • conducted sensitivity analysis;	• hypertension and multifetal gestations are risk factors for placenta accreta, while male fetus and low socioeconomic status are protective factors;
Weiran Zheng, 2020, China	**Retrospective study**	2,219 cases of placenta increta and placenta percreta	• studied and collected cases of placenta increta and placenta percreta obtained from 20 tertiary care centers in China; • collected demographic information, clinical characteristics, and sonographic finding; • confirmed the diagnosis of placental invasion by surgical findings or histopathologic results;	• used logistic regression analysis to determine the risk factors and sonographic features that were significantly associated with a clinical diagnosis of placenta percreta; • generated a formula and subsequent scoring system; • evaluated the scoring system was evaluated using a ROC curve;	• scoring system combining maternal risk factors and ultrasound features can improve the predictive accuracy of placenta percreta and obstetric outcomes
Tian Yang, 2019, China	**Retrospective cohort study**	8,371 singleton pregnancies	• studied women with scarred uterus who were patients at Shengjing Hospital, China Medical University, from January 2013 to December 2017; • the diagnosis of PA was made on clinical grounds • randomly assigned two thirds of the patients to the training set (n =	• performed multivariate logistic regression by using the training set, and developed the nomogram; • performed discrimination and calibration by using both the training and validation sets;	• the incidence of PAS was 5.2%; • the developed nomogram is based mainly on clinical data, and the validation using both the training set and the validation set revealed good discrimination and calibration;

			5,581), and one third to the validation set (n = 2,790).		
Hyo Kyozuka,2019, Japan	**Prospective birth cohort study (nationwide)**	90554 participants (202 cases of PAS)	• identified 90 554 participants treated from 2011 to 2014 in 15 regional centers; • data were obtained from self-reported questionnaires or patient medical records;	• created multiple regression models to identify the risk factors for PAS; • used the chi-square or Fisher exact test to compare the categorical variables, and the t-test to compare the continuous variables after confirming each of the continuous variables was normally distributed; • used the extended Mantel-Haenszel chi-square test of linear trends to analyze proportional trends; • calculated the aOR and 95% CI for PAS using a multiple logistic regression model. • adjusted the analysis for various risk factors;	• placenta previa, assisted reproductive technology-related pregnancy, smoking during pregnancy, repeated cesarean sections, and uterine anomalies were risk factors for PAS in the Japanese population;
Bremen De Mucio, 2019; Uruguay	**Systematic review and meta-analysis**		• searched relevant databases for papers published before August 1, 2018, using terms including “accreta” and “cesarean.” • included cohort studies assessing the risk of placenta accreta according to women's history of uterine surgery.	• performed meta-analyses to assess the risks associated between uterine surgery and placenta accreta, hysterectomy, and uterine rupture. • used the I^2 statistic to examine between-study heterogeneity	• risk of placenta accreta, hysterectomy, and uterine rupture increases with the number of previous cesarean deliveries.
Caiting Chu, 2019, China	**Original Article**	97 patients (42 placenta accreta)	• retrospectively reviewed the clinical characteristics and MRI features of 97 patients from January 2012 to December 2015. • confirmed to be placenta accreta by pathological results or cesarean delivery findings;	• used multivariate logistic regression model for significant differences in variables determined by univariate analysis; • used the Cohen k value to evaluate interobserver agreement in the interpretation of the magnetic resonance images;	• 2 or more instances of previous cesarean deliveries and/or abortion, placenta previa, and placenta myometrial interface interruption were independent risk factors for placenta accreta; • a combination of a single clinical risk factor and an MRI risk factor can improve the diagnosis of placenta accreta;
Prattima Mital, 2019, India	**Retrospective analysis**	81,480 deliveries, of which 74 were identified as PAS	• retrospectively analyzed all patients who delivered with PAS over a 3 year period; • divided the cases into 2 groups - Group 1 consisted of the patients who were diagnosed during the intra partum period and Group 2 was those diagnosed as PAS by	• compared quantitative variables using Independent t test/ Mann-Whitney Test (when the data sets were not normally distributed) • correlated qualitative variables using Chi-Square test/ Fisher’s Exact test;	• incidence of PAS was 0.09% • perinatal mortality was significantly higher in Group 1, meaning antenatal diagnosis of PAS disorders decreases both maternal and perinatal mortality and morbidity.

			• ultrasound in the antepartum period. • maternal and fetal outcomes were compared between the 2 groups.		
Victoria R. Greenberg, 2022, USA	**Retrospective cohort**	252 women, 94 did not have PAS, 67 had focal accreta, and 91 had higher-order PAS	• identified women with PAS diagnosed by ultrasound and/or pathology reports and women with risk factors for PAS (placenta previa, ≥2 prior cesareans or D&Cs, prior myomectomy) at a single tertiary care center from 2008-2021; • excluded women without delivery data or pathology report; • defined the primary outcome as concordance between ultrasound and clinical and pathologic outcome and the secondary outcomes as perinatal morbidities, as well as clinical and sonographic characteristics associated with diagnostic accuracy of PAS;	• assessed Associations by univariate analysis;	• there is high concordance between ultrasound imaging and higher-order PAS but low concordance with focal accreta. • with focal accreta are at risk for perinatal morbidity and deserve further study to improve sonographic detection.;
Ana Pinas Carrillo, 2019, UK	**Review article**		• there has been an exponential increase in the number of cases of PAS disorders in recent years, likely due to an increasing numbers of caesarean section delivery and ART use; • the key to improve maternal and fetal outcomes is prenatal diagnosis; • as the incidence increases, the expertise of clinicians improves, and currently, ultrasound is as good as MRI in diagnosing AIP when performed by an experienced operator;		
Saad El Gelany, 2019, Egypt	**Prospective study**	102 women diagnosed with PAS	• included women diagnosed with PAS disorders admitted to Minia Maternity university hospital, Egypt between January 2017 to August 2018;	• categorized cases into three groups according to the used approach for management: (1) Group (A), (n = 38) underwent cesarean hysterectomy; (2) group (B), (n = 48) underwent cesarean section (CS) with cervical inversion and ligation of both uterine arteries; (3) group (C), (n = 16): the placenta was left in place;	• the incidence of PAS disorders was 0.91%; • maternal age > 32 years, previous C.S. (≥ 2), multiparity (≥ 3) and previous history of placenta previa were risk factor; • the management of PAS disorders should be individualize; • estimated blood loss and blood transfusion in group A were significantly higher than other groups.

Table 1 – General characteristics of the included studies.

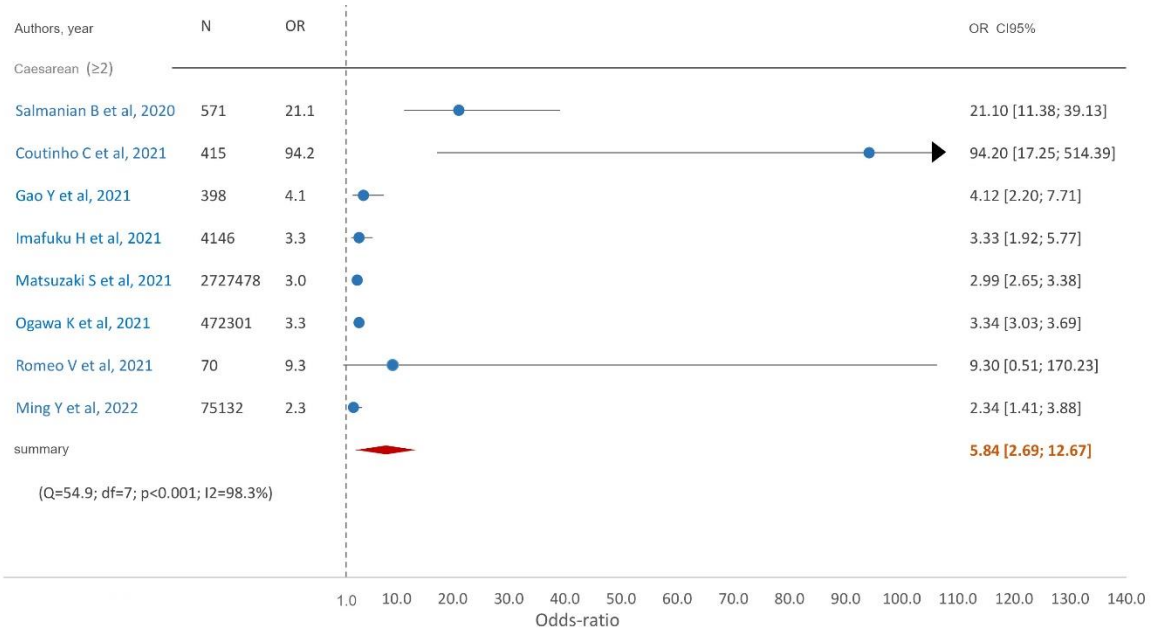

Figure 2 (Figure SIII.2) – Forest plot for the history of a previous cesarian delivery (≥2).

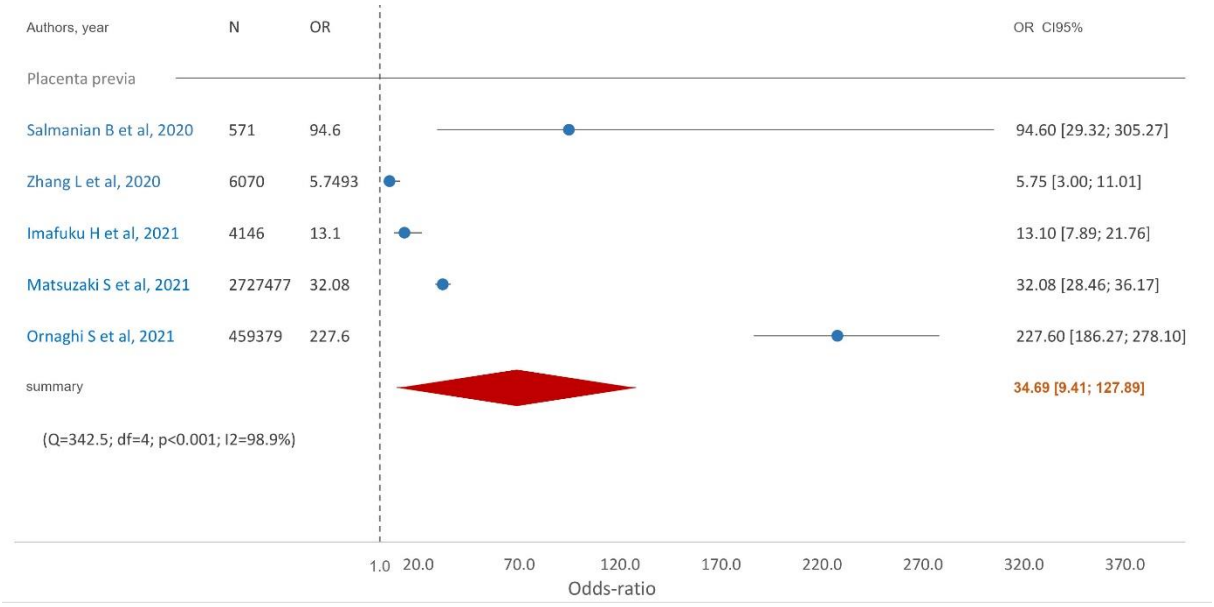

Figure 3 (Figure SIII.3)– Forest plot for placenta previa.

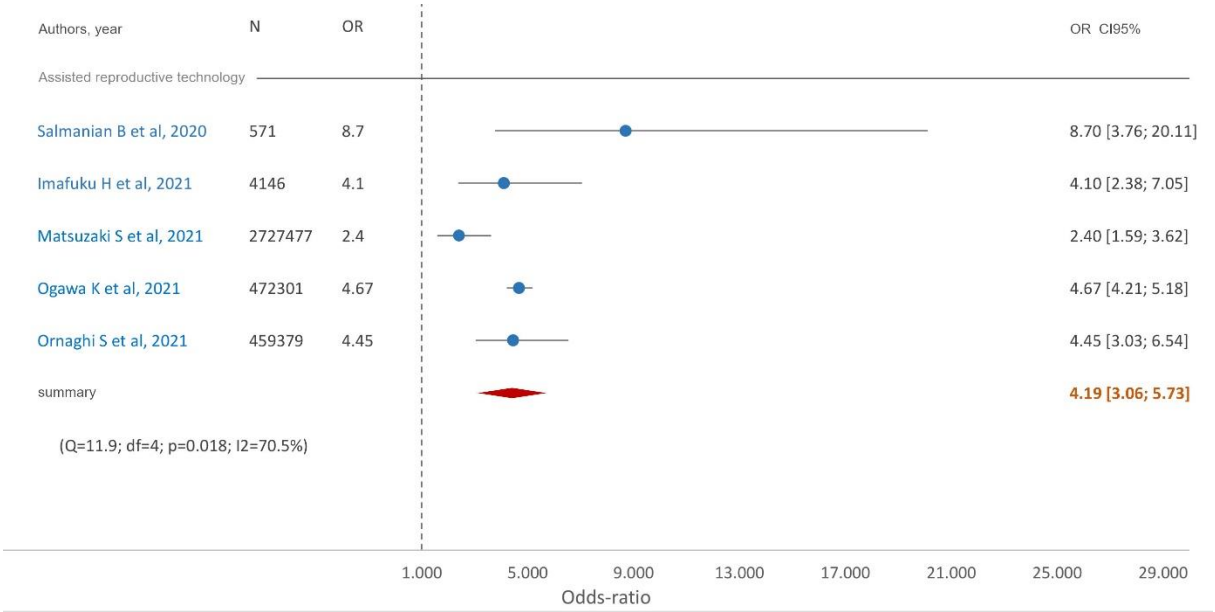

Figure 4 (Figure SIII.5) – Forest plot for assisted reproductive techniques (ART).

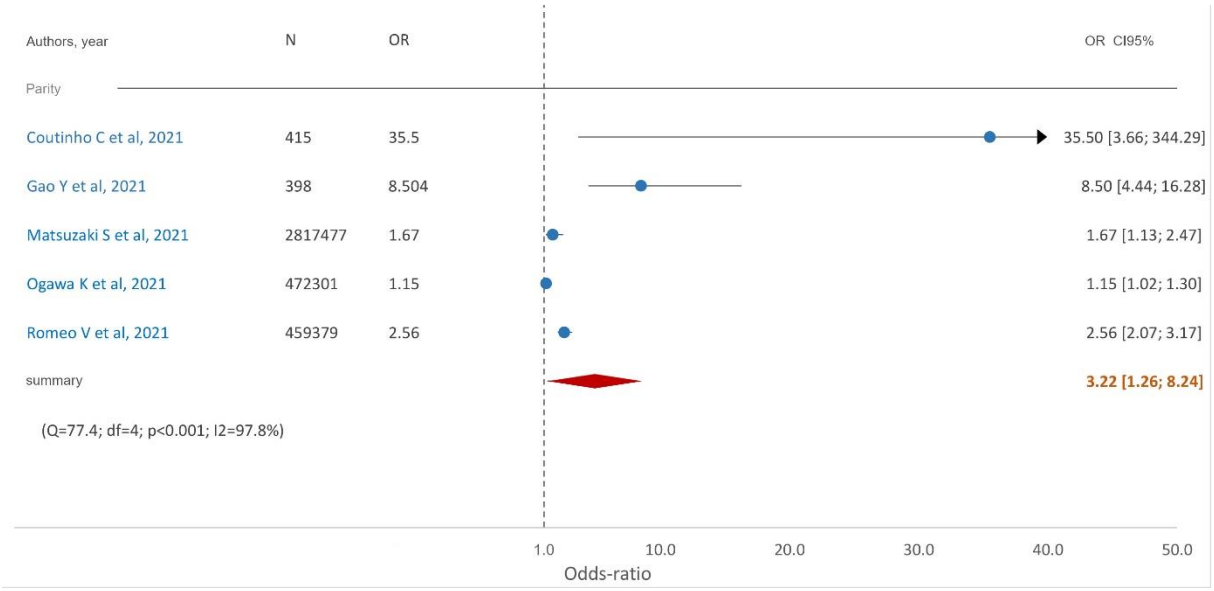

Figure 5 (Figure SIII.6) – Forest plot for multiparity.

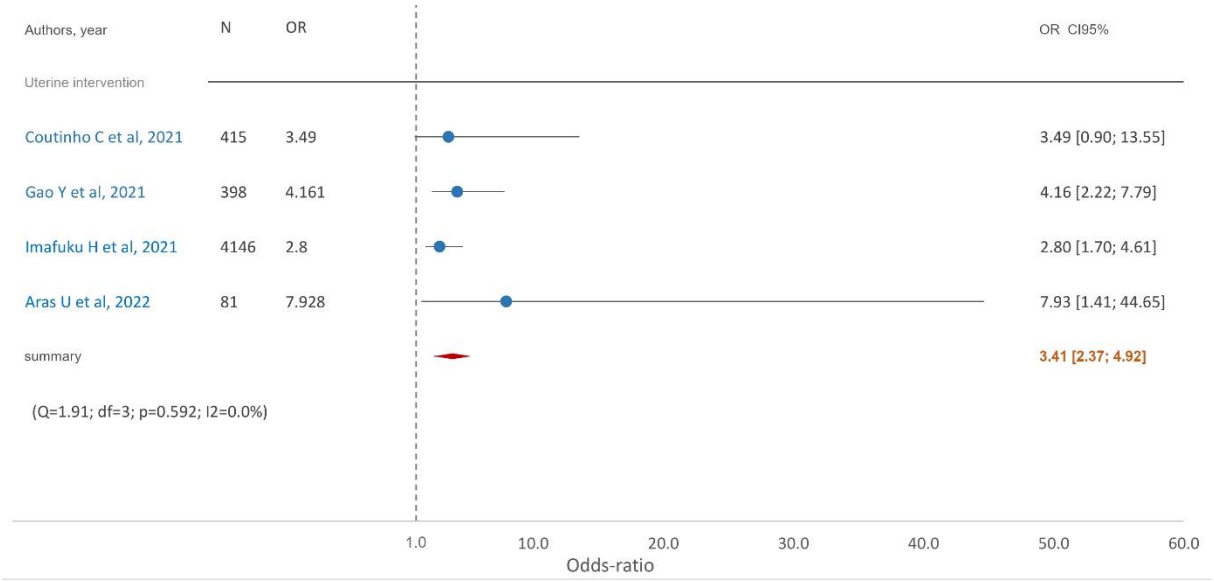

Figure 6 (Figure SIII.7) – Forest plot for previous uterine intervention.

The observed heterogeneity is high in most of our meta-analyses, which can have several explanations, such as differences in the study design, sample size and selection methods, as well as in outcome measures, in each study, and variations in population characteristics, such as demographic, clinical, or social factors.

From the summary measures it is possible to observe that there are statistically significant risk factors and others that are not.

Incidence

All 36 of the included articles had information on the incidence of PAS, of which 9 had values that we were able to use in our meta-analysis, (which can be found in **Figure SIII)**. The graph shows the reported incidence in each study and the summary measure obtained by the random effects model. The aggregate measure was 0.68 (95%CI[0.12%; 1.24%]) The observed heterogeneity was considerable (I^2=99.9%). All but three studies were considered statistically significant, as well as the summary measure.

Previous cesarian delivery

Figure 2 (Figure SIII.2) represents the association between the history of two or more previous cesarian deliveries and PAS. This was the risk factor more often included in the different articles: it was studied in 35 of the 36 articles. Of these, 8 had values that were able to be used in the meta-analysis. Based on the random effect model, the estimated OR was

5.84 (95% CI[2.69; 12.67]). The observed heterogeneity was high (I^2=98.3%). Two of the included studies had very large CI. All but one of the studies were statistically significant individually and the pooled estimate was statistically significant.

Placenta previa

Figure 3 (Figure SIII.3) represents the association between placenta previa and PAS. This was the second most studied risk factor, included in 25 of the 36 articles, 5 of which had information able to be included in the meta-analysis. According to the random effect model, the estimated OR was 34.69 (95% CI: [9.41-; 127.89]). The observed heterogeneity was high (I^2=98.9%). One of the studies had a large CI. All individual studies were statistically significant, as well as the pooled estimate of aggregate measure. The estimate of the aggregate effect was the largest of all the characteristics studied.

Maternal BMI

The association with maternal BMI was also a frequently studied risk factor, included in 25 of the 36 articles. Of these, 4 were included in the meta-analysis.

Two forest plots corresponding to the overweight (BMI 25-29.9kg/m^2) and obesity (BMI > 30kg/m^2) categories, respectively, can be found in can be found in SIIII (**Figures SIII.4a and SIII.4b)**. The reported values should be interpreted in relation to the normal weight (BMI 18.5-24.9kg/m^2), which is the reference.

Only one article had an OR for underweight (BMI <18.5 kg/m^2), so no meta-analysis was performed for this category. Based on each random effect model, the estimated OR was 1.40 (95% CI[0.86; 2.27]) for overweight and 0.99 (95% CI[0-89; 1.10] for obesity. The observed heterogeneity was high for overweight (I^2=94.8%), but significantly lower for obesity (I^2= 18.4%). Of the 4 included studies, only one was considered statistically significant. For both categories, the summary measure results were not statistically significant.

Assisted reproductive techniques (ART)

The association between ART and PAS was analyzed in 18 of the 36 articles, 5 of which were included in our meta-analysis. This association is represented in **Figure 4 (Figure SIII.5).** Based on the random effect model, the estimated OR was 4.19 (95% CI[3.06; 5.73]). The detected heterogeneity was high (I^2=70.5%). There was one study with a large CI. All five of

the included studies were considered statistically significant, as well as the aggregate measure of effect.

Parity

Multiparity as a possible risk factor for PAS was studied in 18 of the 36 articles. Of these, 5 were included in our meta-analysis, represented in **Figure 5 (Figure SIII.6)**. Based on the random effect model, the estimated OR was 3.22 (95% CI[1.26; 8.24]). The detected heterogeneity was considerable (I^2=97.8%). Apart from one, all studies were statistically significant. The aggregate measure of effect was also statistically significant.

Uterine intervention

Of the 36 articles, 19 of them investigated the possible association between the history of a uterine intervention and the development of PAS, 4 of which were ultimately included in our meta-analysis. This association is represented in **Figure 6 (Figure SIII.7).** Based on a random effect model, the estimated OR was 3.41 (95% CI[2.37; 4.92]). There was no heterogeneity found (I^2=0.0%). One of the included studies had a large CI. All but one of the included studies were found statistically significant, as well as the summary measure of effect.

Smoking during pregnancy

The association between PAS and smoking during pregnancy is represented in **Figure SIII.8.** It was explored in 7 of the 36 articles, 3 of which had data that we were able to use in our meta-analysis. Based on each random effect model, the estimated OR was 1.76 (95% CI[0.76; 4.09]). Its heterogeneity was one of the lowest calculated (I^2=53.1%). Although 2 of the 3 studies were considered statistically significant, the pooled effect estimate was not.

Discussion

Our meta-analysis results suggest that of the studied possible associations, placenta previa, a history of 2 or more previous CS, ART, uterine interventions, and multiparity are major risk factors for the development of PAS disorders. The results for maternal BMI and smoking during pregnancy were not statistically significant.

Women with the combination of placenta previa and at least one prior CS have clearly and consistently been identified as a high-risk clinical profile for PAS.[28] Our results support these findings, as these two risk factors had the biggest estimated OR – this means that they were the most significant ones. The work of Conturie and Lyell [29] also found that women with both placenta previa and a history of cesarean delivery are more likely to have a higher grade of invasive PAS. For these reasons, the identification of both these conditions plays a critical role in the diagnosis of PAS, as well as in its optimal management.

Placenta previa had the most substantial result: our results suggest that a pregnancy complicated by this condition is on average 34 times more likely to develop PAS and other studies have also reliably identified previa as an independent risk factor for PAS. It is usually diagnosed during the second or early third trimesters' ultrasound evaluation. Its cause is not yet fully understood, but it is believed to be related to a combination of factors, including advanced maternal age, smoking habits during the gestational period, previous uterine surgery, and a history of a previous cesarean delivery or placenta previa in a previous pregnancy. Moreover, all of these have also been associated with PAS, further corroborating their connection.

Although it is not a preventable condition, its early detection and careful management can help ensure the best possible outcomes for both the mother and the fetus. Women with placenta previa will need careful monitoring throughout pregnancy and may need a cesarean delivery to avoid complications. We support current recommendations to screen all women with placenta previa and risk factors for PAS, between 20 and 24 weeks of gestation [26]. Because missing important signs of placental abnormalities can lead to serious complications, we also attest to the importance of training healthcare providers in all available obstetric imaging techniques. We encourage better, consistent, and standardized training of all screening staff, as they are essential tools for ensuring that pregnancies progress well and that any potential problems are identified early on.

Our results also found that a history of **previous CS** was associated with a 6 times higher risk of developing PAS when compared to women with no previous CS. While we did not study this, other studies have also consistently identified a "dose-dependent" association between a previous CS and PAS[24], highlighting its importance and significance as a major clinical risk

factor. This is a particularly important finding because a history of previous cesarean delivery is the potentially modifiable risk factor most strongly associated with these disorders – hence, by implementing strategies to reduce cesarean delivery rates we will, consequently, also be actively reducing the risk of PAS disorders.

The increased cesarean delivery rates worldwide in recent years are due to a combination of both medical and non-medical factors[31], including (1) maternal request, as more women are requesting cesarean delivery for various reasons, for example, fear of birth, previous negative birth experiences or cultural beliefs; (2) maternal medical conditions, such as hypertension or diabetes, that may require a CS for the safety of the mother and the fetus, and (3) other medical reasons, such as fetal distress, labor dystocia, and multiple gestations.

There are many strategies that can be reinforced in the efforts to reduce cesarean deliveries globally[31,32], we suggest (1) promoting vaginal delivery, by educating pregnant women and healthcare workers about its benefits – this includes promoting vaginal birth after cesarean (VBAC), (2) promoting maternal health, as maintaining maternal health during pregnancy can help prevent complications that may require a cesarean delivery; (3) the encouragement of use of non-pharmacological pain management methods - such as movement and relaxation techniques-, and avoiding unnecessary interventions during labor and delivery, like induction of labor, whenever possible, which may help to reduce the likelihood of CS and (4) improving overall access to quality health care, ensuring that women have access to free and skilled care, not only during the multiple phases of pregnancy, childbirth, and post-delivery but also beyond the gestational period.

When faced with the need for repeat cesarean deliveries, existing research suggests that the adoption of certain surgical techniques – including, but not limited to, gentle tissue handling, effective hemostasis, careful approximation of the myometrium while preserving adequate blood supply, and restoration of normal anatomy - may help to reduce the incidence of long-term complications, as posited by the findings of Sholapurkar *et al.* in 2014. [33]

The research by Kohei Ogawa *et al.* found that the risk factors for PAS differed depending on whether the woman had placenta previa.[34] Among women with placenta previa, the strongest risk factor for PAS was the history of CS, meaning that women who have had a previous cesarean delivery and are also diagnosed with placenta previa are at a higher risk of developing PAS. On the other hand, among women without placenta previa, ART was found to be an important predictor of PAS risk and cesarean section did not appear to be a significant risk factor for PAS in women without placenta previa.

While a history of previous cesarean section and placenta previa are well-known risk factors for PAS, it is important to recognize that other factors can also contribute to its

development. The research by Carusi *et al.* [35] has shown that there may be cases of PAS that are not identified because they do not present with placenta previa and that failure to recognize these cases can result in missed opportunities for delivery planning and increased maternal morbidity[35]. Therefore, it is imperative that healthcare providers remain highly vigilant and consider PAS in women presenting other known associated risk factors.

A recent meta-analysis showed that pregnancies after IVF/ICSI are associated with higher risks of both obstetric and perinatal complications when compared with spontaneous conception, including a significantly increased risk of abnormal placentation, especially for PAS and vasa previa. [36] Our results paralleled this and other recent studies, supporting the hypothesis that **ART** increases the risk of PAS – in our meta-analysis, there was, in average, a more than 4-fold increase.

The incidence of pregnancies resulting from ART is influenced by a variety of factors, such as cultural attitudes toward infertility, the availability of ART services, and the cost of treatment. Still, advances in ART techniques have led to an increase in the number of successful pregnancies and births, further contributing to its overall incidence worldwide. The use of ART has been steadily increasing over the past few decades - according to a 2020 study, it is estimated that ART pregnancies represent 1.5 to 5.9% of all births in high-income countries. Therefore, recognizing its possible consequences is important, even if its mechanisms are still not yet fully comprehended. We recommend adequate pre-conception counseling be provided to women considering undergoing ART as well as close monitoring for these possible complications in pregnancies that resulted from these techniques. Nevertheless, further research is needed to determine which aspect of assisted reproduction technology poses the most risk and how this risk can be minimized.

Our results also supported previous studies that found that **uterine interventions** are associated with an increased risk of PAS, increasing its average likelihood by a factor of 3. This makes sense, as any procedure damaging to the integrity of the uterine lining can theoretically cause PAS. This includes interventions like uterine curettage, manual delivery of the placenta, and postpartum endometritis. More recently, other procedures such as hysteroscopic surgery and endometrial ablation have also been associated with PAS disorders in subsequent pregnancies. [32]

Although we did not include this in our systematic review**, uterine pathologies** such as the bicornuate uterus, adenomyosis, and submucous fibroids, have also been found to be a rare cause of PAS. The study by Kyozuka *et al.* was the first to identify uterine anomalies as a risk factor for PAS[37], in 2019. This finding shows that implantation of placental tissue within the uterine muscle is not always caused by major surgery and may be the reason for rare cases

of PAS disorders seen before the 20th century - when cesarean sections were not as common practice-, and in primigravid women.[2,37] We argue that a medical history positive for these conditions should also be taken into account when evaluating for the risk of PAS.

Our results also suggest that **multiparity** is a significant risk factor for PAS, increasing its average likelihood by a factor of three, and concordant with other studies[32] that also came to this conclusion. Multiple pregnancies can cause changes in the uterine environment, such as uterine scarring or damage to the endometrial lining. Additionally, with each pregnancy, the uterine wall becomes thinner, making it easier for the placenta to invade and grow deeply into the uterus.[1] Therefore, women who have had multiple pregnancies, especially those who have undergone multiple cesarean deliveries, are at a higher risk of developing PAS.

When it comes to **smoking during pregnancy** as a risk factor, our results were not statistically significant. Nonetheless, other studies have found that smoking during pregnancy may increase the risk of PAS[22,38,39,40], because (1) it impairs wound healing of scarred uterus and has been linked to changes in the structure and function of the placenta, which may increase the risk of abnormal placentation and (2) it also increases the risk of placenta previa. [38] In addition, it can also increase the risk of other complications, such as preterm birth and intrauterine growth restriction. Therefore, it is important for obstetricians to counsel pregnant women about the risks of smoking and to support smoking cessation efforts to reduce the risk of PAS and other adverse pregnancy outcomes. Ultimately, we suggest this risk factor should also be considered when assessing the risk for PAS disorders.

Maternal age, hypertension disorders, and multiple gestations did not have data that allowed a meta-analysis to be performed. Still, by reviewing the different articles included in this work, we have some considerations on these risk factors**.**

It is known that women with an **advanced maternal age**, typically defined as 35 years old or older, are at a higher risk of various adverse maternal and neonatal outcomes, including PAS disorders. The work of Humaira Ali *et al.* showed that the odds of PAS increased for every one-year increase in age in women with a previous cesarean.[41] Although these findings may be confounded by higher parity, placenta previa risk, and higher probability of a previous uterine intervention or fertility treatments, it may also represent an altered hormonal and/or implantation environment, as suggested by various studies where advanced maternal age was found to be an independent risk factor for PAS.[26,42,43]

Additionally, even though it can vary depending on the country and region, the average age of women at first birth has been increasing over time – nowadays, women tend to delay childbirth until their late twenties, early thirties, or even later. Thus, as delayed childbearing becomes increasingly more common, the average age at second and third pregnancies also

tends to be higher, hence the importance of addressing maternal age and its possible associated complications during pregnancy and childbirth.

For these reasons, we advise that its potential role in abnormal placentation should also be considered when informing women on reproductive planning and when evaluating the risk for PAS, while keeping in mind that these disorders can present in women of all ages.

The occurrence of PAS has been recently reported to be higher in **multiple gestation** and one of the hypothesized rationales for this association is that there is excessive myometrium stretching and enlargement of the placenta when compared to a singleton pregnancy. [17,44] Although current data on this topic is still scarce, we suggest that pregnant women with multiple pregnancy should be advised to receive prenatal follow-up for PAS during pregnancy.

The data on the association of **hypertensive disorders** and PAS is mixed – some results suggest that it increases the risk of abnormal placentation, as others even identify hypertension as a protective factor[45]. Still, most of the current research suggests that there is an increased risk of PAS in women with hypertensive disorders [40], and that women with PAS are also more likely to develop hypertensive disorders during pregnancy. Because the presence of PAS has also been suggested to increase the risk of adverse outcomes in women with hypertensive disorders, including severe bleeding, need for blood transfusion, and emergency hysterectomy, we recommend that healthcare providers should maintain careful monitoring of these women. We also highlight the need for future research on the association between PAS and hypertensive disorders, for a better understanding of this topic.

Regarding **maternal BMI**, there is some research suggesting that there may be an association between maternal obesity and an increased risk of developing PAS disorders. However, it remains unclear whether this association is independent of confounding factors, such as the higher risk of cesarean delivery commonly observed in obese women. A 2021 multinational database study by Vieira *et al.* found that obesity does not seem to be an independent risk factor for PAS or severity for PAS.[46]

While data on this association are still scarce and uncertain, we suggest that it is crucial to ensure that these women are closely monitored, as high maternal BMI can increase the risk of other various complications for both the mother and the baby, including labor complications that can make the management of a concomitant PAS disorder even more challenging. We also highlight the need for future exploration of this topic.

Additionally, it is important to note that not all cases of adherent placenta require major surgery, and conservative management can be successful in some cases.[4] However, in patients with **adherent placentas requiring manual extraction**, the pathologic finding of focal accreta is associated with an increased risk of hemorrhagic morbidity and retained placenta in

subsequent pregnancies. [47] This means that even if the initial delivery is successful, the risk of complications in future pregnancies is higher if there was evidence of abnormal placental invasion during the previous delivery. [47,48]

Our Clinical Prediction Guideline for PAS

We believe that the key measure in optimizing both prenatal diagnosis and outcomes of women at increased risk for PAS is **the referral of suspected cases,** which implies that healthcare providers should know whom to refer and when to do it – and, thus, profiling women by their clinical risk is crucial.

While there is no standardized qualitative score for PAS, the ACOG recommends using a risk assessment tool to identify women at increased risk for abnormal placentation disorders, where PAS disorders are included. It also recommends using a three-phase classification system to categorize the risk of PAS based on maternal history, placental location, and ultrasound findings.

With this in mind, we aimed to combine our findings and current knowledge of the clinical risk factors associated with PAS into a prediction guideline, to provide recommendations on the best approaches to the screening of PAS. This guideline is presented in **Supplementary Material IV (SIV).**

The guideline defines who needs to be screened, who is responsible for performing the screening, the screening tool to be used and what defines a positive screen test, as well as what should be done with a positive result.

Prenatal visits are essential for ensuring the health and well-being of both the mother and the developing fetus during pregnancy. They provide an opportunity for healthcare providers to monitor the progress of the pregnancy, identify and manage any potential risks or complications and provide guidance on how to maintain a healthy pregnancy. We argue that the already standardized routine prenatal care visits and ultrasounds present an unmissable opportunity to also actively screen for PAS risk factors.

Additionally, important topics can also be discussed and some preventive measures can be taken, such as (1) encouraging vaginal delivery, which includes the promotion of vaginal birth after cesarean (VBAC), by encouraging women with a previous cesarean delivery to attempt a trial of labor for subsequent births, if clinically safe; (2) promoting maternal health, counseling about nutrition, exercise, the risks of smoking, childbirth preparation, and any other concerns the expectant mothers may have, which can help prevent complications, and (3)

improving overall access to quality health care, including prenatal, intrapartum, and postpartum care, which can also help to decrease the likelihood of complications associated with PAS.

Our guideline proposes a score that considers the different relative clinical importance of each risk factor, attributing points according to its clinical significance. Still, while this classification system provides a general outline for assessing the risk of PAS, it is essential to recognize that specific risk factors may have differing levels of significance in predicting the development of PAS. Thus, we reinforce the idea that healthcare providers should carefully evaluate each patient's obstetric history and risk factors to determine their individual risk for PAS and tailor management accordingly.

We suggest the routine mid-pregnancy transabdominal obstetric ultrasound, performed between 18-20 weeks of gestation to determine placenta location, should include screening for both placenta previa and PAS signals. The choice of ultrasound technique should be based on the specific clinical scenario and the healthcare provider’s judgment. Ultimately, if a pregnancy complicated by placenta previa is identified, women should undergo regular serial ultrasound examinations during the second and third trimesters of pregnancy, to confirm a persistent previa and identify possible signs associated with PAS.

If the screening identifies a high-risk profile, we recommend immediate referral of the woman to a specialized diagnostic center, with experience in PAS disorders, to ensure the best possible outcome for the mother and fetus.

A screening test is a powerful tool for identifying potential health problems before they become life-threatening conditions, which in turn can reduce the associated healthcare costs. This approach to preventive care is essential to improving overall health equity by increasing access to affordable healthcare services.

Our guideline can be carried out by any healthcare provider, in both a primary care setting and a medical facility with limited resources, and it does not necessarily require additional medical appointments beyond those that are already scheduled for prenatal general care.

Nevertheless, it will need validation, that can be performed using simulation tests and, thus, has the potential to become a great clinical instrument in the near future.

Conclusion

Healthcare professionals should thoroughly assess all pregnant women for known risk factors for PAS disorders. Our results show that placenta previa, history of two or more previous cesarean sections, assisted reproductive technology, uterine interventions, and multiparity are the most significant ones. Moreover, women with both placenta previa and at least two prior CS are at the highest risk of PAS.

An efficient and organized screening program for PAS is crucial in referring medical settings, as it would enable early detection and referral of high-risk women to PAS diagnostic centers. A high level of suspicion is necessary for early diagnosis, and in this profiling the women with known relevant risk factors is essential - careful evaluation of obstetric history and other maternal clinical risk factors plays a crucial part, complementing imaging techniques.

Several measures can be taken to reduce the risk of PAS disorders in high-risk pregnancies. Some of these include (1) preconception counseling for women with known risk factors, as it can help identify and address modifiable risk factors and optimize maternal and fetal outcomes; (2) limiting the number of cesarean deliveries: women and healthcare providers should be counseled on the risks of cesarean deliveries and the potential benefits of vaginal birth after cesarean for future pregnancies (3) avoiding unnecessary uterine interventions, such as curettage or myomectomy, when possible.

Cesarean sections are the most important potentially modifiable risk factor for PAS disorders - it is vital to reduce the rate of cesarean deliveries globally because unnecessary cesarean deliveries can lead to increased maternal and neonatal morbidity and mortality, longer hospital stays, higher healthcare costs, and future reproductive risks for women.

Safe and effective care of a woman with a PAS disorder depends on a timely diagnosis. Our results directly impact the ability of screening and, thus, improve the management of women at risk for this potentially life-threatening condition.

By allowing delivery planning and timing, with care provided by a multidisciplinary team of healthcare providers, based on the extent and severity of placental invasion, this will help to minimize the risk of maternal hemorrhage and other complications.

Lastly, several areas in PAS disorders require further research to improve our understanding and management of this condition, including the development of effective prevention strategies, identification of reliable biomarkers, additional investigation on some potential risk factors, and a better understanding of its long-term implications, including future pregnancy outcomes and potential long-term complications.

Strengths and Limitations

This study aimed to improve our understanding of which women are most likely to develop PAS and to create a practical screening guideline that could be easily interpreted and implemented. Its main strength is that the triage of women we suggest is possible in a primary care setting and low-resource medical settings with basic obstetric facilities, not necessarily requiring additional visits beyond those that are already routinely indicated.

Nevertheless, there were some limitations to our work. As PAS disorders are a growing obstetric issue, more studies are being published every year. However, this is still a relatively rare diagnosis and published literature is often difficult to manage and interpret, due to problems with the heterogeneity in the definition, terminology, and criteria for diagnosis. This could explain the wide variability in the prevalence of the different degrees of abnormal placentation, in the accuracy of prenatal diagnosis, as well as why prenatal detection rates remain low.

Our meta-analysis was complicated by heterogeneous subsets of women and methodology across studies. High heterogeneity can make it challenging to draw definitive conclusions and may require additional methods such as subgroup analysis or meta-regression to try and identify sources of heterogeneity and explore potential reasons for the variation in effect sizes between studies.

Furthermore, since the sum of patients was small for some of the studied risk factors found in these studies, conclusions should be interpreted with caution. Additionally, of the 36 ultimately included studies, 18 were retrospective, limiting the overall quality of the analysis, as there are some biases inherent to this study design, such as the selection, information and recall bias.

Overall, we argue that all these reasons emphasize the need for a standardized and consensual method for diagnosing and reporting PAS. Future research with prospective designs and data collection plans can provide higher-level evidence, although we understand their difficulty in this context.

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References

1. Casanova R. Beckmann and Ling's Obstetrics and Gynecology, 8th edition; Section II: Obstetrics, Chapter 5: Maternal-Fetal Physiology (pages 43-55); 2019

2. Jauniaux E, Ayres-de-Campos D, Duncombe G, Klaritsch P, Chantraine F, Kingdom J, et al. FIGO consensus guidelines on placenta accreta spectrum disorders: Introduction. International Journal of Gynecology and Obstetrics. 2018;140(3):261–4. Available from: https://doi.org/10.1002/ijgo.12406

3. Morlando M, Collins S. Placenta accreta spectrum disorders: Challenges, risks, and management strategies. Int J Womens Health. 2020;12:1033–45. Available from: https://doi.org/10.2147/IJWH.S224191

4. Jauniaux E, Bhide A, Kennedy A, Woodward P, Hubinont C, Collins S, et al. FIGO consensus guidelines on placenta accreta spectrum disorders: Prenatal diagnosis and screening. International Journal of Gynecology and Obstetrics. 2018;140(3):274–80. Available from: http://dx.doi.org/10.1002/ijgo.12408

5. Silver RM. Official reprint from UpToDate: Placenta accreta spectrum: Management [Internet]. 2021. Available from: https://www.uptodate.com/contents/placenta-accreta-spectrum-management/print?source=history_widgetwww.uptodate.com

6. Silver MR. Official reprint from UpToDate: Placenta accreta spectrum: Clinical features, diagnosis, and potential consequences [Internet]. 2021. Available from: https://www.uptodate.com/contents/placenta-accreta-spectrum-clinical-features-diagnosis-and-potential-consequences/print?source=history_wid…1/32www.uptodate.com

7. Goulding AN, Casey S, Reed CC, Shamshirsaz AA, Lombaard H, Belfort MA, et al. Perinatal mental healthcare utilization among patients with placenta accreta spectrum. Am J Obstet Gynecol [Internet]. 2023;228(1):S257. Available from: https://doi.org/10.1016/j.ajog.2022.11.465

8. Gao Y, Gao X, Cai J, Han F, Xu G, Zhang X, et al. Prediction of placenta accreta spectrum by a scoring system based on maternal characteristics combined with ultrasonographic features. Taiwan J Obstet Gynecol [Internet]. 2021;60(6):1011–7. Available from: https://doi.org/10.1016/j.tjog.2021.09.011

9. O'Brien JM, Barton JR, Donaldson ES. The management of placenta percreta: Conservative and operative strategies. Am J Obstet Gynecol. 1996;175(6):1632–8. Available from http://dx.doi.org/10.1016/s0002-9378(96)70117-5

10. Thang NM, Anh NTH, Thanh PH, Linh PT, Cuong TD. Emergent versus planned delivery in patients with placenta accreta spectrum disorders: A retrospective study. Medicine (United States). 2021;100(51):E28353. Available from http://dx.doi.org/10.1097/MD.0000000000028353

11. Zhong W, Zhu F, Li S, Chen J, He F, Xin J, et al. Maternal and Neonatal Outcomes After Planned or Emergency Delivery for Placenta Accreta Spectrum: A Systematic Review and Meta-Analysis. Front Med (Lausanne). 2021;8(September). Available from: http://dx.doi.org/10.3389/fmed.2021.731412

12. ACOG Obstetric Care Consensus No. 9: Levels of Maternal Care: Correction. Obstetrics & Gynecology [Internet]. 2023;141(4). Available from:

https://journals.lww.com/greenjournal/Fulltext/2023/04000/ACOG_Obstetric_Care_Consensus_No__9__Levels_of.33.aspx

13. Silver RM, Ware Branch D. Placenta Accreta Spectrum. Obstet Gynecol Surv. 2018;73(9):515–7. Available from: http://dx.doi.org/10.1056/NEJMcp1709324

14. Guzmán López JA, Gutiérrez Sánchez LÁ, Pinilla-Monsalve GD, Timor-Tritsch IE. Placenta accreta spectrum disorders in the first trimester: a systematic review. J Obstet Gynaecol (Lahore) [Internet]. 2022;42(6):1703–10. Available from: https://doi.org/10.1080/01443615.2022.2071151

15. Svanvik T, Jacobsson AK, Carlsson Y. Prenatal detection of placenta previa and placenta accreta spectrum: Evaluation of the routine mid-pregnancy obstetric ultrasound screening between 2013 and 2017. International Journal of Gynecology and Obstetrics. 2022 Jun 1;157(3):647–53. Available from: http://dx.doi.org/10.1002/ijgo.13876

16. Kolarova T, Simon R, MacKinnon H, Burns RN, Olerich K, Katz R, et al. 646 Characterizing placenta accreta spectrum in patients without prior cesarean delivery. Am J Obstet Gynecol [Internet]. 2021;224(2):S406. Available from: http://dx.doi.org/10.1016/j.ajog.2020.12.670

17. Cali G, Labate F, Cucinella G, Fabio M, Buca D, Di Girolamo R, et al. Placenta accreta spectrum disorders in twin pregnancies as an under-reported clinical entity: a case series and systematic review. Journal of Maternal-Fetal and Neonatal Medicine [Internet]. 2022;35(25):8848–51. Available from: https://doi.org/10.1080/14767058.2021.2005568

18. Mittal P, Suri J, Pruthi N, Pandey D, Bharti R. Comparison of placenta accreta spectrum disorders diagnosed in the intrapartum and antepartum period— A three-year experience in a tertiary referral unit of India. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2019 May 1;236:41–5. Available from: http://dx.doi.org/10.1016/j.ejogrb.2019.03.001

19. Mittal P, Suri J, Pruthi N, Pandey D, Bharti R. Comparison of placenta accreta spectrum disorders diagnosed in the intrapartum and antepartum period— A three-year experience in a tertiary referral unit of India. European Journal of Obstetrics and Gynecology and Reproductive Biology [Internet]. 2019;236:41–5. Available from: https://doi.org/10.1016/j.ejogrb.2019.03.001

20. Hecht JL, Baergen R, Ernst LM, Katzman PJ, Jacques SM, Jauniaux E, et al. Classification and reporting guidelines for the pathology diagnosis of placenta accreta spectrum (PAS) disorders: recommendations from an expert panel. Modern Pathology. 2020 Dec 1;33(12):2382–96. Available from: http://dx.doi.org/10.1038/s41379-020-0569-1

21. Hecht JL, Baergen R, Ernst LM, Katzman PJ, Jacques SM, Jauniaux E, et al. Classification and reporting guidelines for the pathology diagnosis of placenta accreta spectrum (PAS) disorders: recommendations from an expert panel. Modern Pathology. 2020 Dec 1;33(12):2382–96. Available from: http://dx.doi.org/10.1038/s41379-020-0569-1

22. Coutinho CM, Giorgione V, Noel L, Liu B, Chandraharan E, Pryce J, et al. Effectiveness of contingent screening for placenta accreta spectrum disorders based on persistent low-lying placenta and previous uterine surgery. Ultrasound in Obstetrics and

Gynecology. 2021 Jan 1;57(1):91–6. Available from: http://dx.doi.org/10.1002/uog.23100

23. Zheng W, Zhang H, Ma J, Dou R, Zhao X, Yan J, et al. Validation of a scoring system for prediction of obstetric complications in placenta accreta spectrum disorders. Journal of Maternal-Fetal and Neonatal Medicine [Internet]. 2022;35(21):4149–55. Available from: https://doi.org/10.1080/14767058.2020.1847077

24. Ornaghi S, Maraschini A, Donati S, Donati S, Maraschini A, D'Aloja P, et al. Characteristics and outcomes of pregnant women with placenta accreta spectrum in Italy: A prospective population-based cohort study. PLoS One [Internet]. 2021;16(6 June):1–16. Available from: http://dx.doi.org/10.1371/journal.pone.0252654

25. Schwickert A, van Beekhuizen HJ, Bertholdt C, Fox KA, Kayem G, Morel O, et al. Association of peripartum management and high maternal blood loss at cesarean delivery for placenta accreta spectrum (PAS): A multinational database study. Acta Obstet Gynecol Scand. 2021;100(S1):29–40. Available from: http://dx.doi.org/10.1111/aogs.14103

26. Badr DA, Al Hassan J, Salem Wehbe G, Ramadan MK. Uterine body placenta accreta spectrum: A detailed literature review. Placenta [Internet]. 2020;95(April):44–52. Available from: https://doi.org/10.1016/j.placenta.2020.04.005

27. Ornaghi S, Maraschini A, Donati S, Donati S, Maraschini A, D'Aloja P, et al. Characteristics and outcomes of pregnant women with placenta accreta spectrum in Italy: A prospective population-based cohort study. Vol. 16, PLoS ONE. Public Library of Science; 2021. Available from: http://dx.doi.org/10.1371/journal.pone.0252654

28. Kayem G, Seco A, Beucher G, Dupont C, Branger B, Crenn Hebert C, et al. Clinical profiles of placenta accreta spectrum: the PACCRETA population-based study. BJOG. 2021;128(10):1646–55. Available from: http://dx.doi.org/10.1111/1471-0528.16647

29. Conturie CL, Lyell DJ. Prenatal diagnosis of placenta accreta spectrum. Curr Opin Obstet Gynecol. 2022;34(2):90–9. Available from: http://dx.doi.org/10.1097/GCO.0000000000000773

30. Salmanian B, Fox KA, Arian SE, Erfani H, Clark SL, Aagaard KM, et al. In vitro fertilization as an independent risk factor for placenta accreta spectrum. Am J Obstet Gynecol [Internet]. 2020;223(4):568.e1-568.e5. Available from: https://doi.org/10.1016/j.ajog.2020.04.026

31. WHO recommendations on non-clinical interventions to reduce unnecessary cesarean sections. Available from: https://www.who.int/publications/i/item/9789241550338

32. De Mucio B, Serruya S, Alemán A, Castellano G, Sosa CG. A systematic review and meta-analysis of cesarean delivery and other uterine surgery as risk factors for placenta accreta. Vol. 147, International Journal of Gynecology and Obstetrics. John Wiley and Sons Ltd.; 2019. p. 281–91. Available from: http://dx.doi.org/10.1002/ijgo.12948

33. Sholapurkar SL. Surgical techniques at cesarean might modify placenta accreta risk. BJOG: An International Journal of Obstetrics and Gynecology. 2014 Jan;122(1). Available from: http://dx.doi.org/10.1111/1471-0528.13017

34. Ogawa K, Jwa SC, Morisaki N, Sago H. Risk factors and clinical outcomes for placenta accreta spectrum with or without placenta previa. Arch Gynecol Obstet [Internet]. 2022;305(3):607–15. Available from: https://doi.org/10.1007/s00404-021-06189-2

35. Carusi DA, Fox KA, Lyell DJ, Perlman NC, Aalipour S, Einerson BD, et al. Placenta Accreta Spectrum Without Placenta Previa. Obstetrics and gynecology. 2020;136(3):458–65. Available from: http://dx.doi.org/10.1097/AOG.0000000000003970

36. Vestal NL, Mandelbaum RS, Matsuzaki S, Sangara RN, Bainvoll L, Ouzounian JG, et al. Assisted Reproductive Technology and Increased Abnormal Placentation: a Population-Based Analysis. Fertil Steril [Internet]. 2021;116(3):e230. Available from: https://doi.org/10.1016/j.fertnstert.2021.07.623

37. Kyozuka H, Yamaguchi A, Suzuki D, Fujimori K, Hosoya M, Yasumura S, et al. Risk factors for placenta accreta spectrum: Findings from the Japan environment and Children's study. BMC Pregnancy Childbirth. 2019;19(1):1–7. Available from: http://dx.doi.org/10.1186/s12884-019-2608-9

38. Kyozuka H, Yamaguchi A, Suzuki D, Fujimori K, Hosoya M, Yasumura S, et al. Risk factors for placenta accreta spectrum: Findings from the Japan environment and Children's study. BMC Pregnancy Childbirth. 2019 Nov 27;19(1). Available from:

39. Matsuzaki S, Mandelbaum RS, Sangara RN, McCarthy LE, Vestal NL, Klar M, et al. Trends, characteristics, and outcomes of placenta accreta spectrum: a national study in the United States. Am J Obstet Gynecol. 2021 Nov 1;225(5):534.e1-534.e38. Available from: http://dx.doi.org/10.1016/j.ajog.2021.04.233

40. Hou YP, Lommel L, Wiley J, Zhou XH, Yao M, Liu S, et al. Influencing factors for placenta accreta in recent 5 years: a systematic review and meta-analysis. Journal of Maternal-Fetal and Neonatal Medicine [Internet]. 2022;35(11):2166–73. Available from: https://doi.org/10.1080/14767058.2020.1779215

41. Ali H, Chandraharan E. Etiopathogenesis and risk factors for placental accreta spectrum disorders. Vol. 72, Best Practice and Research: Clinical Obstetrics and Gynaecology. Bailliere Tindall Ltd; 2021. p. 4–12. Available from: 10.1016/j.bpobgyn.2020.07.006

42. El Gelany S, Mosbeh MH, Ibrahim EM, Mohammed M, Khalifa EM, Abdelhakium AK, et al. Placenta Accreta Spectrum (PAS) disorders: Incidence, risk factors and outcomes of different management strategies in a tertiary referral hospital in Minia, Egypt: A prospective study. BMC Pregnancy Childbirth. 2019;19(1):1–8. Available from: 10.1186/s12884-019-2466-5.

43. Ogawa K, Jwa SC, Morisaki N, Sago H. Risk factors and clinical outcomes for placenta accreta spectrum with or without placenta previa. Arch Gynecol Obstet. 2022 Mar 1;305(3):607–15. Available from: http://dx.doi.org/10.1007/s00404-021-06189-2

44. Guo Z, Han X, Zheng W, Yang H, Ma J. Placenta Accreta Spectrum Among Multiple Gestation: A Retrospective Analysis Based on a Chinese Population. Front Endocrinol (Lausanne). 2022;13(May):1–7. Available from: http://dx.doi.org/10.3389/fendo.2022.862785

45. Jenabi E, Salimi Z, Salehi AM, Khazaei S. The environmental risk factors prior to conception associated with placenta accreta spectrum: An umbrella review. J Gynecol Obstet Hum Reprod [Internet]. 2022;51(7):102406. Available from: https://doi.org/10.1016/j.jogoh.2022.102406

46. Vieira MC, Rijken MJ, Braun T, Chantraine F, Morel O, Schwickert A, et al. The relation between maternal obesity and placenta accreta spectrum: A multinational database

study. Acta Obstet Gynecol Scand. 2021;100(S1):50–7 Available from: http://dx.doi.org/10.1111/aogs.14075

47. Mullen CR, Battarbee AN, Ernst LM, Peaceman AM. Focal Placenta Accreta: Risk Factors, Adverse Obstetrical Outcomes, and Recurrence in Subsequent Pregnancies [10L]. Obstetrics & Gynecology [Internet]. 2017;129(5). Available from: https://journals.lww.com/greenjournal/Fulltext/2017/05001/Focal_Placenta_Accreta__Risk_Factors,_Adverse.444.aspx

48. Erfani H, Salmanian B, Aagaard KM, Fox KA, Meshinchiasl N, Shamshirsaz AA, et al. 1131 Microscopic placenta accreta as a risk factor for placenta accreta spectrum in a subsequent pregnancy. Am J Obstet Gynecol [Internet]. 2021;224(2):S697–8. Available from: http://dx.doi.org/10.1016/j.ajog.2020.12.1155

Supplementary material

SUPPLEMENTARY MATERIAL I (SI)

SEARCH STRATEGY

REVIEW QUESTION: What is the clinical profile of the woman at increased risk of Placenta Accreta Spectrum (PAS)?

The search was conducted in three databases – PubMed, Embase and The Cochrane Library –, with the following search phrases:

- **PubMed's Search:** (placenta increta) OR (placenta percreta) OR (placenta accreta) AND (risk factors)
- **Embase's Search:** (placenta accreta spectrum) AND (clinical risk factors)
- **The Cochrane Library's Search**: (placenta accreta spectrum) AND (clinical risk factors)

PICO principles

P-POPULATION

- **MeSH terms:** pregnancy, pregnant women
- **Synonyms:**
  - Pregnancies* OR
  - Gestation* OR
  - (Pregnant AND Woman*) OR
  - (Pregnant AND Women*)

I-INTERVENTION

- **MeSH terms:** cesarian delivery, placenta previa, maternal age, multiparity, uterine intervention, assisted reproductive techniques
- **Synonyms:**
  - (Cesarean AND Sections*) OR
  - (Delivery AND Abdominal*) OR
  - (C-Section (OB)*) OR
  - (Maternal AND Age*) OR
  - Uteri* OR
  - Womb* OR
  - (Uterine AND Myomectomies*) OR
  - (Assisted AND Reproductive AND Techniques*)

C-COMPARISON

- **MeSH terms:** placenta accreta spectrum, placenta accreta, placenta increta, placenta percreta
- **Synonyms:**
  - Placentation* OR
  - (Placentation AND Abnormalities*) OR
  - (Placenta AND Diseases*) OR
  - (Pregnancy AND complications*) OR
  - (Placental AND Development*)
  - (Placenta AND Accreta*) OR
  - (Placenta AND Percreta*) OR
  - (Placenta AND Increta*) OR

O-OUTCOME

- **MeSH terms:** prenatal diagnosis, prenatal screening, maternal mortality, hysterectomy, postpartum hemorrhage, maternal morbidity;
- **Synonyms:**
  - (Prenatal AND Diagnosis*) OR
  - (Intrauterine AND Diagnosis*) OR
  - (Antenatal AND Diagnosis*) OR
  - (Fetal AND Screening*) OR
  - (Fetal AND Diagnosis*) OR
  - (Fetal AND Imaging*) OR
  - (Pregnancy AND Outcomes*) OR
  - (Prenatal AND Care*) OR
  - (Antenatal AND Care*) OR
  - (Obstetric AND Labor AND Complications*) OR
  - (Maternal AND Mortality*) OR
  - (Postpartum AND Immediate AND Hemorrhage*) OR
  - (Postpartum AND Hemorrhage*)

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SUPPLEMANTARY MATERIAL II (SII)

QUALITY ASSESSMENT

SYSTEMATIC-REVIEWS AND META-ANALYSIS

CRITERIA	Ensiyeh Jenabim, 2022	Julieth López, 2022	Giuseppe Cali, 2022	Yi-Ping Hou, 2020	Bremen De Mucio, 2019
1. Is the review based on a focused question that is adequately formulated and described?	Yes	Yes	Yes	Yes	Yes
2. Were eligibility criteria for included and excluded studies predefined and specified?	Yes	Yes	Yes	Yes	Yes
3. Did the literature search strategy use a comprehensive, systematic approach?	Yes	Yes	Yes	Yes	Yes
4. Were titles, abstracts, and full-text articles dually and independently reviewed for inclusion and exclusion to minimize bias?	Yes	Yes	NC	Yes	Yes
5. Was the quality of each included study rated independently by two or more reviewers using a standard method to appraise its internal validity?	Yes	Yes	NC	Yes	Yes
6. Were the included studies listed along with important characteristics and results of each study?	Yes	Yes	No	Yes	Yes
7. Was publication bias assessed?	Yes	Yes	NC	Yes	Yes
8. Was heterogeneity assessed? (applies only to meta-analyses)	Yes	NC	NC	Yes	Yes
Quality Rating (Good, Fair, or Poor)	☺ Good	☺ Good	--- Fair	☺ Good	☺ Good

Table 1 - Quality Assessment for included Systematic Reviews and Meta-analysis, performed following an adapted version of the "Quality Assessment of Systematic Reviews and Meta-Analysis tool by the American National Heart, Lung and Blood Institute (NHLBI)". (NC = not clear) Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

REVIEW ARTICLES

CRITERIA	ARTICLES		
	Dominique A. Badr, 2020	Charlotte L, 2022	Ana Pinas Carrillo, 2019
1) JUSTIFICATION OF THE ARTICLE'S IMPORTANCE FOR THE READERSHIP	2/2	2/2	2/2
2) STATEMENT OF CONCRETE AIMS OR FORMULATION OF QUESTIONS	2/2	2/2	1/2
3) DESCRIPTION OF THE LITERATURE SEARCH	2/2	0/2	0/2
4) REFERENCING	2/2	2/2	2/2
5) SCIENTIFIC REASONING	2/2	2/2	2/2
6) APPROPRIATE PRESENTATION OF DATA	2/2	2/2	2/2
OVERALL QUALITY	☺ **Good**	- Fair	- Fair

Table 2 - Quality Assessment for included Review articles, performed following the "SCALE FOR THE ASSESSMENT OF NARRATIVE REVIEW ARTICLES (SANRA)". Available from: https://researchintegrityjournal.biomedcentral.com/articles/10.1186/s41073-019-0064-8

OBSERVATIONAL STUDIES AND ORIGINAL ARTICLES

CRITERIA	Tian Yang, 2019	Hyo Kyozuka, 2019	Caiting Chu, 2019	Prattima Mital, 2019	Daniela Carusi, 2022	Weiran Zheng, 2020	: Ülkü Aras, 2022
1. Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	-	Yes	Yes
3. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Was a sample size justification, power description, or variance and effect estimates provided?	-	Yes	Yes	-	-	Yes	No
5. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	Yes	Yes	Yes	Yes	Yes	No
6. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	Yes	Yes	-	Yes	-	Yes
7. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Yes	-	Yes	Yes	Yes	Yes	Yes
8. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	-	-	Yes	Yes	-	-	Yes
9. Was the exposure(s) assessed more than once over time?	No	-	No	-	-	-	Yes
10. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants	Yes	-	-	Yes	Yes	Yes	
11. Were the outcome assessors blinded to the exposure status of participants?	No	No	No	NO	No	No	No
12. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Yes	Yes	Yes	No	-	No	Yes
QUALITY RATING (Good, Fair, or Poor)	☺ **Good**	☺ **Good**	☺ **Good**	☺ **Good**	☺ **Good**	☺ **Good**	☺ **Good**

CRITERIA	Hadi Erfani, 2021	Nicole Vistal, 2021	Teodora Kolarova, 2021	Victoria Greenberg, 2022	Zhirong Guo, 2022	Saad El Gelany, 2019	Rhiannon Heading, 2021	Yanhong Ming, 2022
1. Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Was a sample size justification, power description, or variance and effect estimates provided?	Yes	No	no	No	NC	Yes	no	yes
5. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	Yes	Yes	Yes	Yes	no	No	No
6. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	-	No	No	No	No	No	Yes	Yes
8. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Was the exposure(s) assessed more than once over time?	No	No	No	No	No	NC	No	No
10. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants	Yes	Yes	Yes	NC	Yes	Yes	Yes	Yes
11. Were the outcome assessors blinded to the exposure status of participants?	No	No	No	No	No	No	No	No
12. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Yes	Yes	No	No	Yes	No	No	Yes
QUALITY RATING (Good, Fair, or Poor)	☺ **Good**	☺ **Good**	☺ **Good**	☺ **Good**	☺ **Good**	☺ **Good**	☺ **Good**	☺ **Good**

CRITERIA	Sara Ornaghi, 2021	Shinya Matsuzaki, 2021	G Kayem, 2021	Satya Dutta, 2020	C.M. Coutinho, 2021	Bahram Salmanian, 2020	Ysu Gao, 2021
1. Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes	Yes	-	Yes	Yes	Yes
3. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	-	Yes	Yes	Yes	Yes	No
4. Was a sample size justification, power description, or variance and effect estimates provided?	-	Yes	-	Yes	Yes	-	No
5. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	No	Yes	-	-	-	Yes	No
6. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	Yes?	-	-	Yes	Yes	Yes
7. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Yes	-	Yes	-	Yes	Yes	Yes
8. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	-	Yes	Yes	Yes	Yes	Yes	Yes
9. Was the exposure(s) assessed more than once over time?	-	-	No	No	Yes	-	No
10. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants	Yes	-	Yes	No	Yes	Yes	Yes
11. Were the outcome assessors blinded to the exposure status of participants?	-	-	-	-	-	-	-
12. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	No	Yes	No	No	Yes	Yes	Yes
QUALITY RATING (Good, Fair, or Poor)	☺ **Good**	☺ **Good**	☺ **Good**	- Fair	☺ **Good**	☺ **Good**	☺ **Good**

CRITERIA	Nguyen Manh Thang, 2021	Panchan Zheng, 2022	Kohei Ogawa, 2021	Teresia Svanvik, 2021	Hitomi Imafuku, 2021	Valeria Romeo, 2021
1. Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes	Yes	NC	Yes	Yes
3. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	Yes	Yes	Yes	Yes	Yes
4. Was a sample size justification, power description, or variance and effect estimates provided?	Yes	Yes	Yes	NC	NC	Yes
5. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	-	No	Yes	No	Yes	-
6. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	Yes	Yes	Yes	Yes	Yes
7. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Yes	No	No	No	No	Yes
8. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes
9. Was the exposure(s) assessed more than once over time?	-	-	-	-	-	-
10. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants	Yes	Yes	Yes	Yes	Yes	Yes
11. Were the outcome assessors blinded to the exposure status of participants?	No	No	No	No	No	Yes
12. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	-	Yes	-	Yes	Yes	Yes
QUALITY RATING (Good, Fair, or Poor)	☺ **Good**	☺ **Good**	☺ **Good**	☺ **Good**	☺ **Good**	☺ **Good**

Table 3 - Quality Assessment for the included Observational Studies and Original Articles, performed following an adapted version of the "Quality Assessment of Observational Studies tool by the American National Heart, Lung and Blood Institute (NHLBI)". (NC=not clear; "-": does not apply).Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

SUPPLEMENTARY MATERIAL III

META-ANALYSIS – FOREST PLOTS FOR THE INCIDENCE OF PAS AND EACH STUDIED CLINICAL RISK FACTOR

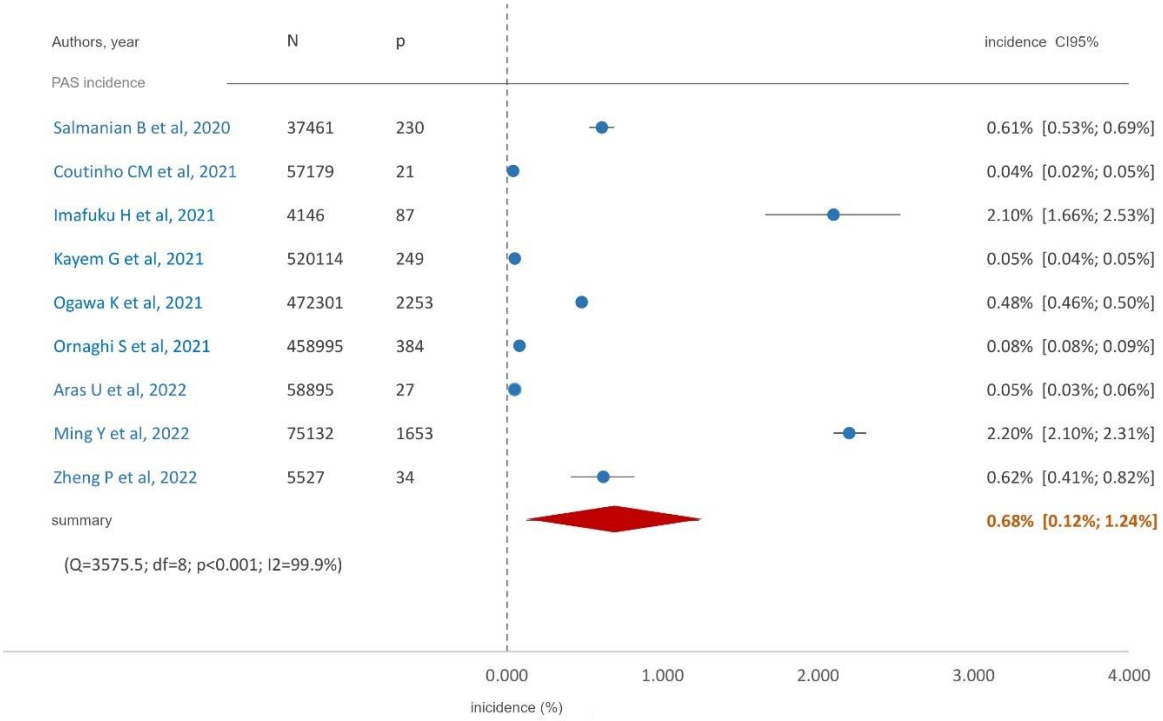

Figure SIII.1 – Forest plot for the incidence of PAS.

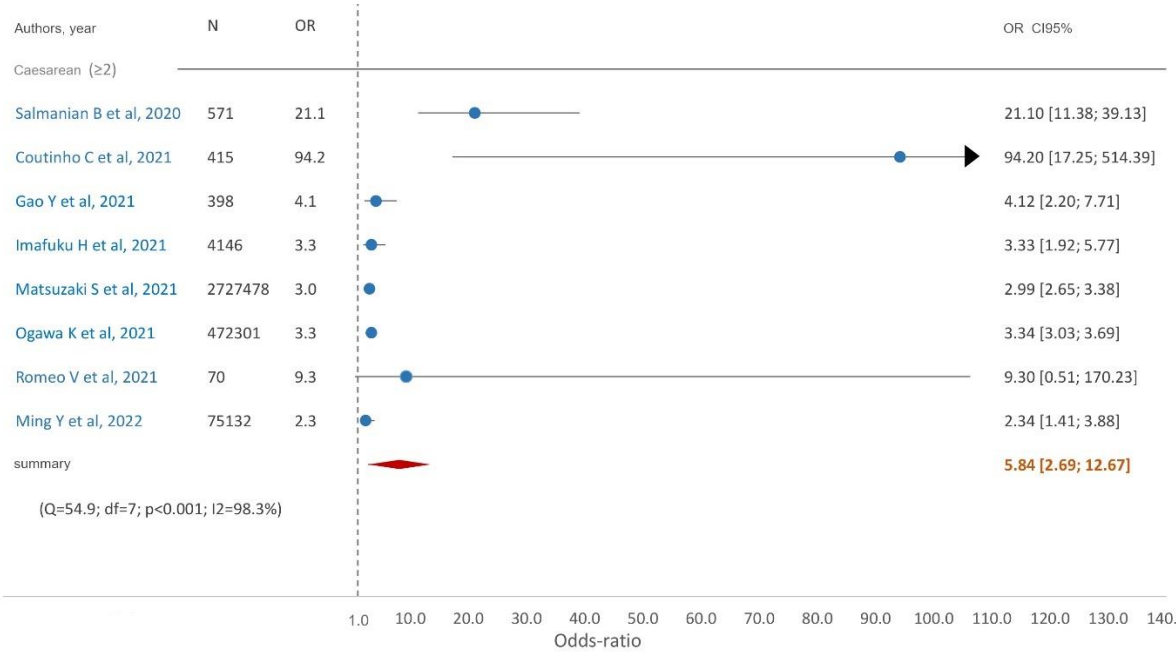

Figure SIII.2 – Forest plot for history of a previous cesarian delivery (≥2).

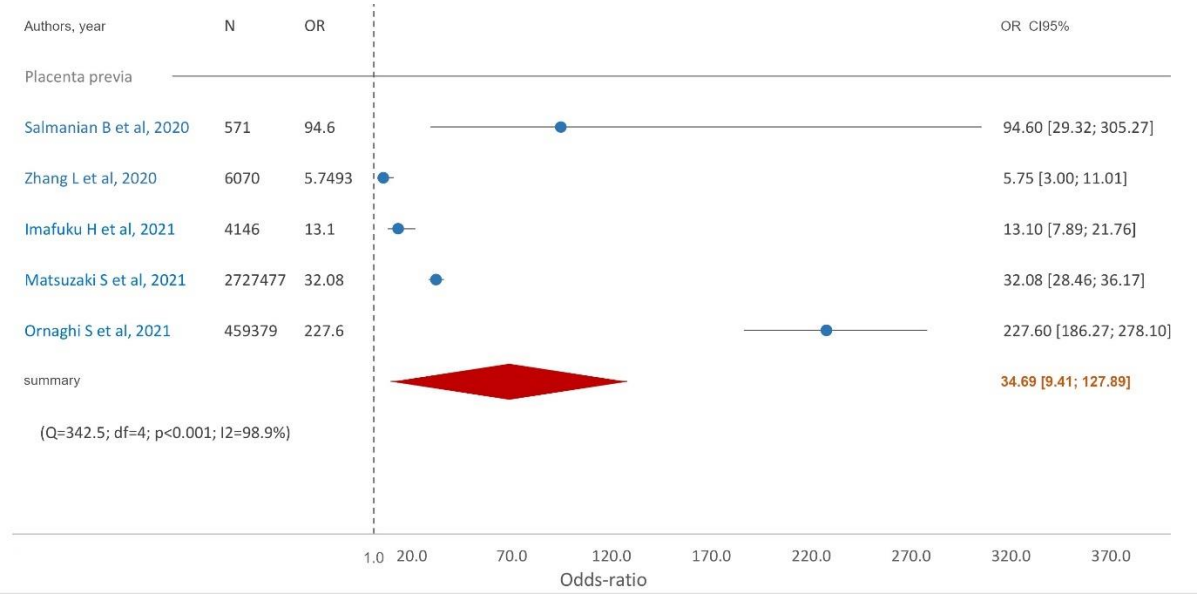

Figure SIII.3 – Forest plot for placenta previa.

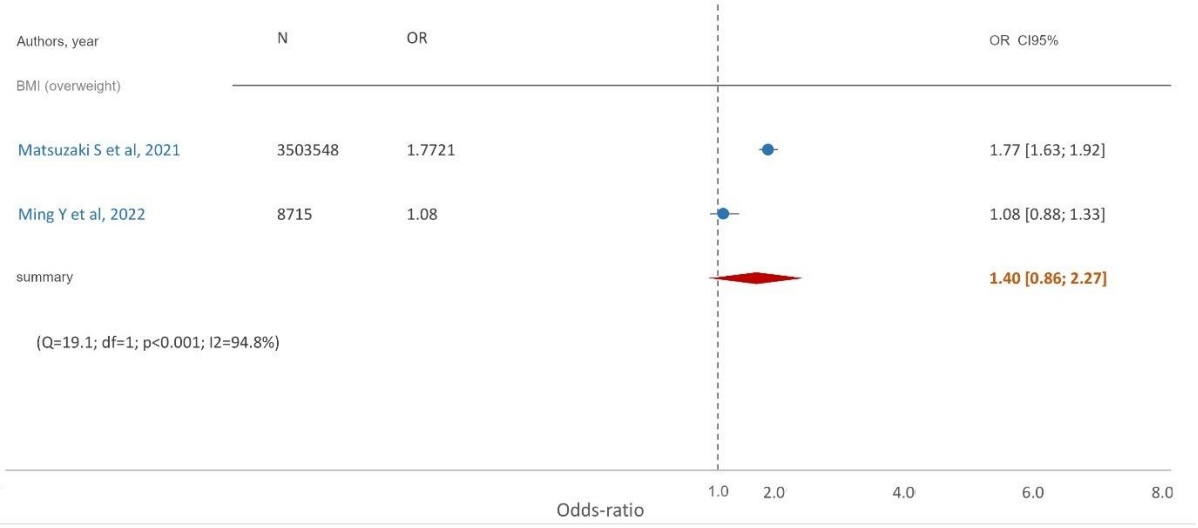

Figure SIII.4a – Forest plot for maternal BMI: overweight category (BMI 25-29.9kg/m^2).

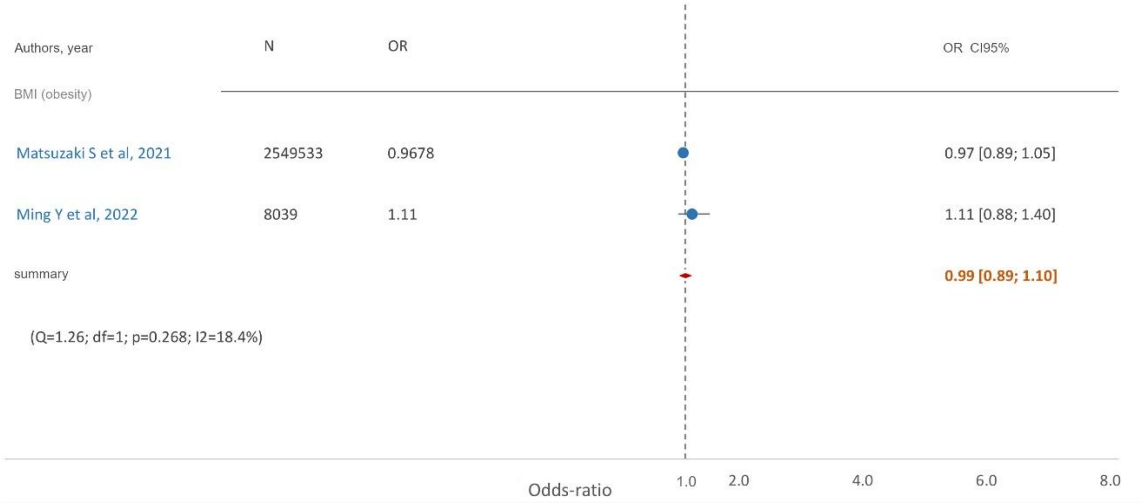

Figure SIII.4b – Forest plot for maternal BMI: obesity category (BMI 18.5-24.9kg/m^2).

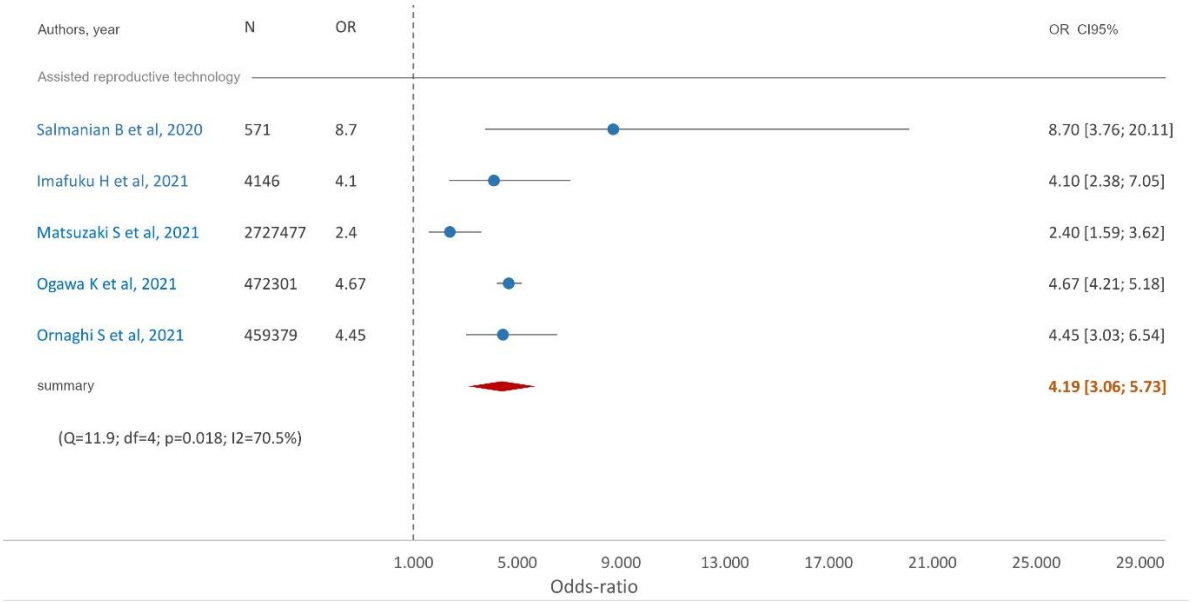

Figure SIII.5 – Forest plot for assisted reproductive techniques (ART).

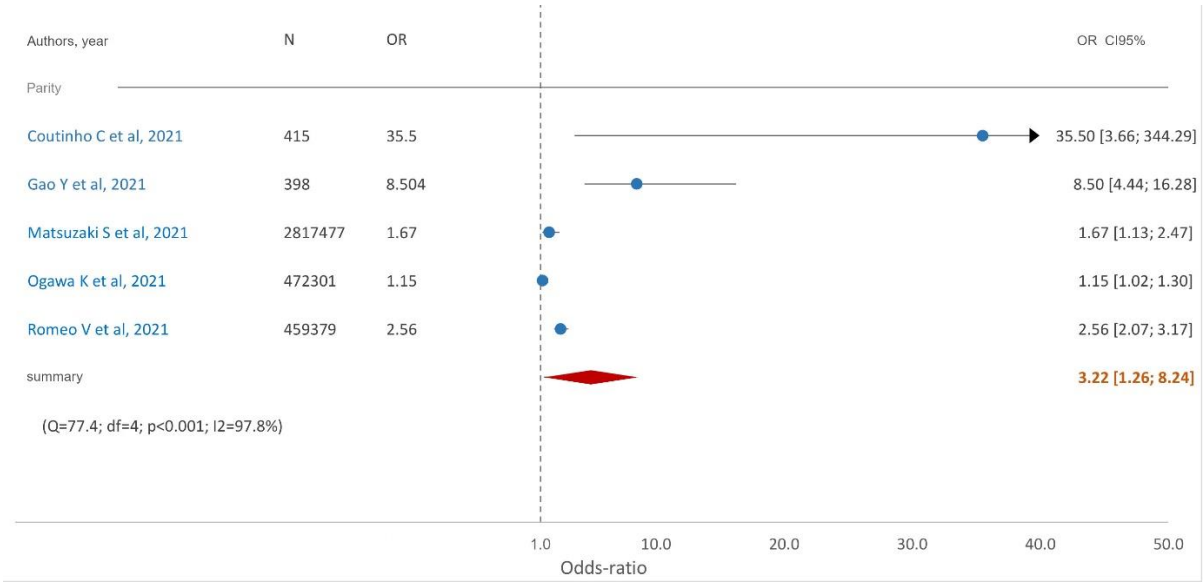

Figure SIII.6 – Forest plot for multiparity.

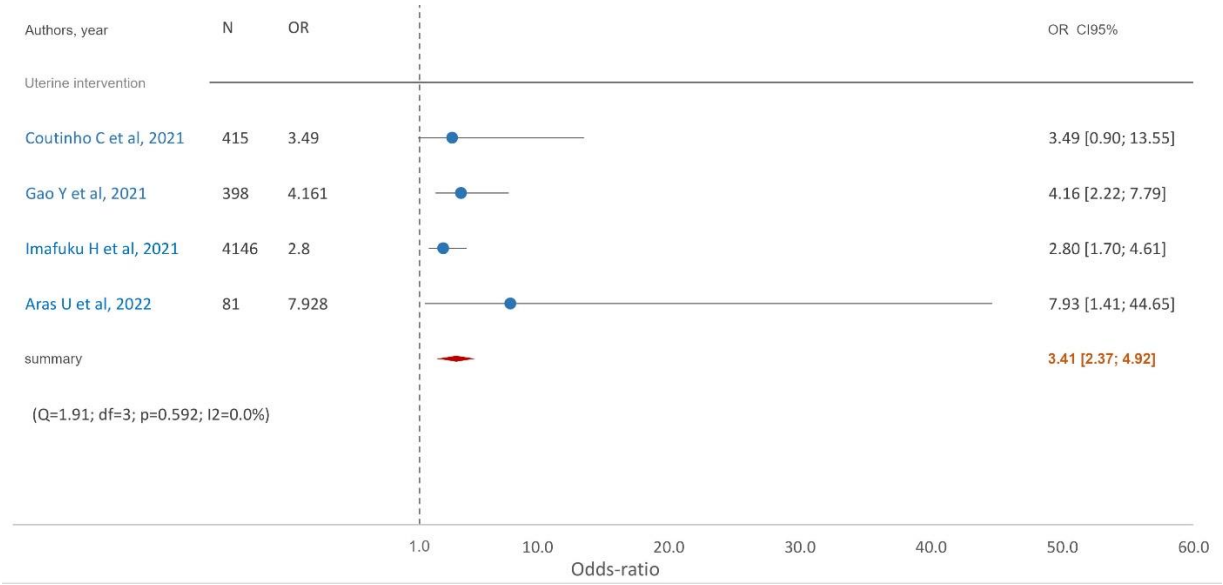

Figure SIII.7 – Forest plot for previous uterine intervention.

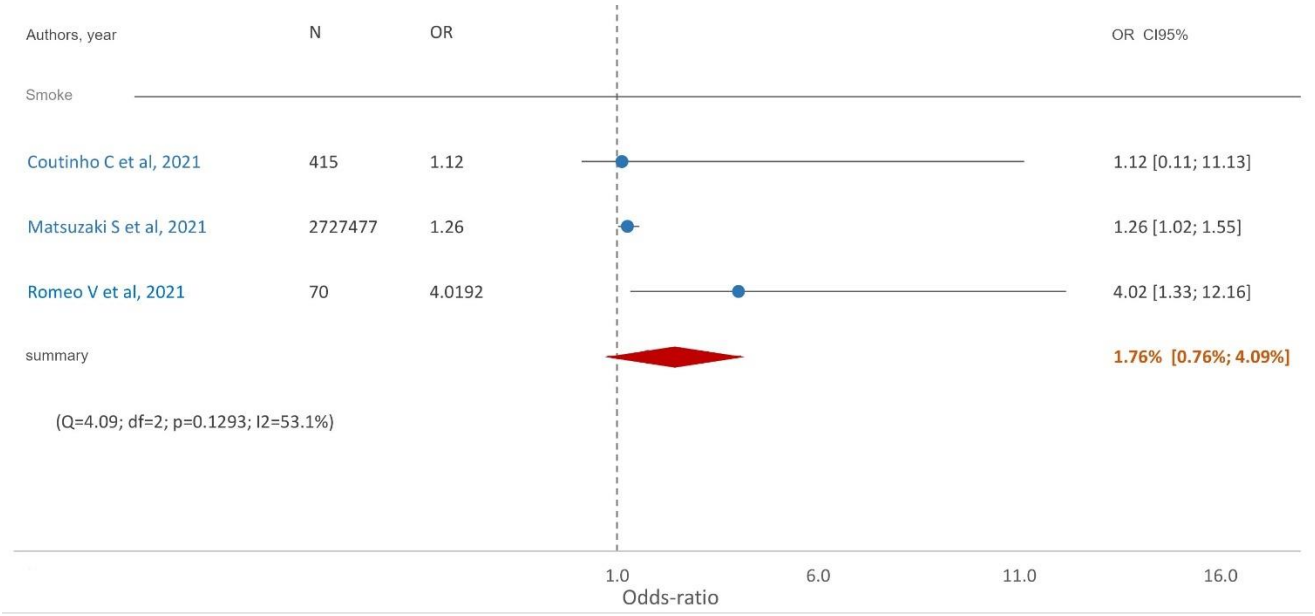

Figure SIII.8– Forest plot for smoking during pregnancy.

SUPPLEMENTARY MATERIAL IV

Guideline for Placenta Accreta Spectrum Disorders' Screening According to the Woman's Clinical Risk Profile

Prenatal visits are essential for ensuring the health and wellbeing of both the mother and the developing baby during pregnancy. They provide an unmissable opportunity for healthcare providers to screen women for risk factors associated with PAS disorders.

Considering the ACOG recommendations for using a risk assessment tool to identify women at increased risk for abnormal placentation disorders and their suggested three-tiered classification system to categorize the risk of PAS, as wells as current knowledge on PAS risk factors, we propose the approach presented below for a standardized initial screening of pregnant women.

INITIAL APPROACH

1) WHEN SHOULD THE SCREENING BEGIN?

- We suggest that the already standardized routine prenatal care visits and ultrasounds present an unmissable opportunity to also actively screen for PAS risk factors;
- It should be routinely implemented in every prenatal care visit;
- Additionally, preventive measures can be taken and will ideally start during pre-conceptional counselling:
    - encourage vaginal delivery, which includes the promotion of vaginal birth after cesarean (VBAC), by encouraging women with a previous cesarean delivery to attempt a trial of labor for subsequent births, if clinically safe;
    - promote maternal health, which can help prevent complications that may require a cesarean delivery;
        - counsel about nutrition and exercise and the risks of smoking; support smoking cessation efforts to reduce the risk of PAS and other adverse pregnancy outcomes;
        - counsel women considering undergoing ART;
        - address the role of maternal age on reproductive planning and outcomes;
    - improve overall access to quality health care, which can also help to decrease the likelihood of conditions associated with PAS;

2) **WHO SHOULD BE SCREENED?**

- All pregnant patients should be screened;

3) **WHO IS RESPONSIBLE FOR PERFORMING THIS SCREENING?**

- This screening process can be carried out by any healthcare provider, in a primary care setting or in a medical facility that may have limited resources and basic obstetric facilities;
- It does not necessarily require additional medical appointments beyond those that are already scheduled for prenatal general care;

4) **WHAT SHOULD THE SCREENING TOOL BE?**

- We propose starting by implementing the checklist suggested in **Table V.1** and acting according to its final score.
    - it considers the different relative clinical importance of each risk factor – the most significant ones were attributed more points;
- We suggest that the routine mid-pregnancy transabdominal obstetric ultrasound, performed between 18-20 weeks, to determine placenta localization, should include screening for placenta previa and PAS associated signs;
    - the choice of ultrasound technique should be based on the specific clinical scenario and the judgement of the healthcare provider.

5) **WHAT SHOULD BE DONE WITH THE SCREENING SCORE?**

LOW RISK CLINICAL PROFILE (< 2 points)

- We suggest maintaining a screening program similar to any other pregnant woman;

INTERMEDIATE RISK CLINICAL PROFILE (score 2-6 points)

- If a pregnancy complicated by placenta previa is suspected or identified – we suggest women should undergo regular serial ultrasound examinations during the second and third trimesters of pregnancy, to confirm a persistent previa and;
- We suggest healthcare providers continue to screen for risk factors and any other alterations during every prenatal visit and during routine ultrasounds;

HIGH RISK CLINICAL PROFILE (score ≥ 6 points)

- If the screening identifies a high-risk clinical profile, we recommend immediate referral to a specialized ultrasound diagnostic center, experienced in PAS disorders, to ensure the best possible outcome for the mother and baby.

RISK FACTOR	ACTION
☐ **Combination of history of ≥1 previous cesarian section + placenta previa in the current pregnancy**	Add 6 points
☐ **History of ≥ 1 previous cesarian section**	Add 2 points Add an additional 1 point for each previous cesarean delivery
☐ **Placenta previa in the current pregnancy**	Add 2 points
☐ **History of previous manual removal of placenta**	Add 1 point
☐ **Use of assisted reproductive techniques (ART)**	Add 1 point
☐ **History of uterine intervention** • previous uterine surgery • dilation and curettage • endometritis • hysteroscopic surgery • endometrial ablation	Add 1 point
☐ **Multiparity**	Add 1 point
☐ **Smoking during pregnancy**	Add 1 point
☐ **Multiple gestation**	Add 1 point
☐ **Advanced maternal age (>35 years)**	maintain active surveillance
☐ **Hypertensive disorders**	
☐ **Overweight or obese (maternal BMI >25 kg/m^2)**	

ADDED FINAL SCORE AND RESPECTIVE CLINICAL PROFILE

- **SCORE OF < 2 POINTS →** Low risk clinical profile
- **SCORE OF 2-6 POINTS →** Intermediate risk clinical profile
- **SCORE OF ≥ 6 POINTS →** High risk clinical profile

Table IV.1 – Clinical risk factors to consider and respective final risk clinical profile for PAS disorders