Title: Placenta accreta spectrum - variations in clinical practice and maternal morbidity between UK and France: a population-based comparative study

Running title: Variation in management of placenta accreta spectrum between UK and France.

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Abstract. (Words: 250/250)

Objective: To compare the management and outcomes of women with Placenta Accreta Spectrum (PAS) in France and the UK.

Design: Two population-based cohorts.

Setting: All obstetrician-led hospitals in the UK and maternity hospitals in eight French regions.

Population: Two-hundred and nineteen women with PAS in France and one-hundred and thirty-four women in the UK.

Methods: The management and outcomes of women with PAS were compared between the UK and France.

Main outcome measures: Median blood loss, severe postpartum haemorrhage (≥3 litres), postpartum infection and damage to surrounding organs.

Results: The management differed between the two countries; a larger proportion of women with PAS in UK had a caesarean hysterectomy compared to France (43% vs. 26%, P<0.001), while in France, a larger proportion of women with PAS had a uterus conserving approach compared to the UK (36% vs. 19%, <0.001). The 24-hour median blood loss in the UK was 3 litres (IQR:1.7-6.5) compared to 1 litre (IQR:0.5-2.5) in France; more women in the UK had a severe PPH compared to women with PAS in France (58% vs. 21%, P<0.001). There was no difference between the UK and French populations for postpartum infection or organ damage.

Discussion: UK and France have very different approaches to managing PAS, with more women in France receiving a uterine conserving and more women undergoing caesarean hysterectomy in the UK. A life-threatening haemorrhage was more common in the UK than in France, which may be the result of differential management and/or the organisation of healthcare systems.

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Key words: Placenta accreta spectrum, management, haemorrhage, hysterectomy, conservative management

Tweetable abstract: In women with placenta accreta spectrum, severe haemorrhage was more common in UK vs. France.

Introduction

Placenta accreta spectrum (PAS) includes placenta accreta, increta, and percreta and is traditionally characterised histologically by a total or partial absence of decidua and placental adherence to or invasion of the myometrium.[1] PAS becomes a clinical problem after birth when the placenta does not physiologically detach from the uterus and forcible placental removal is followed by massive obstetric haemorrhage (MOH) leading to further morbidity and risk of maternal death.[2-4] PAS incidence has accelerated in recent decades,[5-7] simultaneously with the rise in caesarean section rates, which have surpassed 30% in many high-resource countries.[8-10]

Early detection and a planned management have been associated with improved maternal outcomes. Antenatal detection of PAS is critical to the prevention of maternal morbidity arising from PAS as it[11, 12] enables appropriate management through a multi-disciplinary team within a well-equipped tertiary centre with experience in managing the complexity presented by PAS.[11-14] The management of PAS can be broadly subdivided into two main approaches: conservative approaches or caesarean hysterectomy. However, comparison of these approaches for women with PAS has not been robustly investigated.[15-17]

Caesarean hysterectomy is considered the standard approach to manage PAS[11, 18] and forms the mainstay of the management of PAS by many authorities and clinicians internationally, including in the UK.[3] Previous studies have shown caesarean hysterectomy to be lifesaving treatment for women where other uterus conserving surgeries fail.[19, 20] Others have used an approach to conserve the uterus where the placenta is left in situ either partially or completely without attempted removal.[17, 21] This approach is the most common method of conservative management.[22] Given the rarity, potential severity and heterogeneity in management, a randomized controlled trial would be extremely difficult to perform in this area. Therefore, an international comparison between countries with different management policies of PAS may help to answer whether a conservative approach is effective and safe.

Currently, a uterine conserving approach is frequently used in women with PAS in France. French guidelines propose the two options: treatment to conserve the uterus or caesarean hysterectomy.[23] Conversely, UK guidelines recommend caesarean-hysterectomy as the standard management and leaving the placenta in situ only for women desiring uterine preservation or when the surgical team considers caesarean-hysterectomy inappropriate.[24] This cross-country variation offers an opportunity to study and compare the outcomes from two countries. This study aimed to compare the management and maternal outcomes in women with PAS in France and the UK.

Methods

Study population

This was a binational population-based secondary analysis study of PAS using data from two population-based cohort studies from the UK [25] and France.[26, 27, 28] The data were collected nationally in the UK and from eight regions within France. Data were prospectively collected using a national obstetric surveillance system in the UK (UKOSS) and a prospective cohort study in France (PACCRETA).

UKOSS (UK)

The UK data were collected using the UKOSS system and the UKOSS methods have been previously described.[29] In brief, women meeting the case definition were identified nationally in the UK during the period of May 2010 to April 2011. Women with PAS were identified using the case definition in Table 1. Anonymised data were collected using a paper data collection form and a nominated reporter in each maternity hospital in the UK completed this form using the woman's hospital records. The UKOSS data have been published previously.[3, 25]

PACCRETA (France)

The methodology of the PACCRETA study has been described in the published protocol.[26] In summary, this population-based study identified women meeting the case definition (Table 1) during the period of November 2013 to October 2015, from 176 centres across eight regions of France where there were 520,114 maternities, which represents 30% of the national total over the study period. Each centre had a nominated clinician that identified women who met the case definition. In addition, delivery suite logs and electronic records were checked to maximise case ascertainment. Data collected from the medical records of each woman were entered onto a web-based data collection form.[27]

Case definitions

The individual studies' case definitions for France and the UK differed. A common case definition was devised to provide a harmonised dataset of women with PAS, which involved selecting women in France that met the stricter UKOSS definition (Box 1).

Specific classification for variables

Information on comparability of the dataset is available in the supplementary section. The grading of PAS (accreta, increta and percreta) was classified into two categories: placenta percreta and a category containing both placenta increta and accreta, on the basis these are often largely indistinguishable clinically and as some women were treated with a leaving in situ approach with no histological uterine examination when a hysterectomy was avoided. Any history of uterine surgery was combined into a variable that included previous caesarean section, myomectomy, cavity breach, dilation and curettage, previous surgical termination of pregnancy and evacuation of retained products of conception. Uterotonics for treatment of haemorrhage included oxytocin, ergometrine, misoprostol, sulprostone and other synthetic prostaglandins

Management, maternal and infant outcomes

Conservative management was defined as placenta left in situ, either completely or partially in women who did not have a caesarean hysterectomy. Surgical management for haemorrhage included hysterectomy, pelvic arterial embolisation, uterine balloon tamponade and other conservative surgeries included uterine compression sutures and arterial ligation. Hysterectomy was categorised into total hysterectomy (occurring at any point), caesarean hysterectomy (occurring after a caesarean section within 4 hours of birth for the UK women and verified as a caesarean hysterectomy from the operative report for the French women) and hysterectomy after placenta left-in-situ (conservative approach). Planned hysterectomy was indicated in the medical notes if hysterectomy had been planned before delivery. Time of hysterectomy was also available in both datasets.

The outcomes were median estimated total blood loss, severe postpartum haemorrhage (≥3000 millilitres (mls)), major postpartum haemorrhage (≥2000mls), red blood cell (RBC) transfusion, massive blood transfusion (≥6 units of RBC), damage to the bowel, urinary tract or bladder, postpartum infection, Intensive Therapy Unit (ITU) admission and maternal death [30]. Damage to the urinary tract, bowel or bladder was combined into one category. Postpartum infection and damage to surrounding organs were extracted from free text in response to the question of "did woman have any other morbidity?" in the UK and the French data were based on specific questions. The primary infant outcome was perinatal death.

Missing data

Women in France who did not have a postpartum haemorrhage did not have a blood loss value entered; the estimated blood loss for French women without a PPH was imputed to be 500mls, as above this threshold, a PPH would have been recorded in the data collection form.[23] In addition, this avoided possible bias towards French management.

Statistical analysis

Between country analysis

The incidence of PAS was calculated per 10,000 maternities according to the estimated number of maternities (UK), and the reported number of maternities from each maternity unit in France, which occurred during the study period. The confidence intervals were estimated using the exact binomial distribution.

A comparative analysis was undertaken in women who had PAS in both France and the UK. The women's characteristics, medical history, obstetric and haematological management and perinatal and maternal outcomes were compared between France and the UK. Normality was assessed using histograms. Normally distributed continuous variables were presented as means with standard deviations and skewed continuous variables were presented as medians with interquartile ranges. The following statistical tests were used where appropriate: student's t-test, Wilcoxon rank-sum

test, Kruskal-Wallis test, and chi-square tests or the Fisher's exact test. A p-value <0.05 was used to determine statistical significance.

Sensitivity analyses were undertaken to assess results in sub-populations, which included women who had placenta percreta, PAS suspected antenatally, and women with placenta praevia detected antenatally. All statistical analyses were conducted using STATA version 15.1 (Stata Corp LLC, College Station, TX, USA).

Patient and public involvement

The patients and public were involved in the design and interpretation of the UKOSS placenta accreta study as part of the UKOSS Steering Committee. There was no patient and public involvement in the PACCRETA study.

Results

The derived study population in the UK and France is shown in Figure 1. In the UK, there were 134 women with PAS who met the case definition during the period May 2010 to April 2011, in 798,634 maternities. This gave an estimated incidence of PAS in 1.7 women per 10,000 maternities (95%CI: 1.4-2.0). After harmonisation of definitions, 219 women in the PACCRETA study met the same case definition over a two-year period in 2013-2015, among 520,114 maternities. This gave an estimated incidence of PAS of 4.2 women per 10,000 maternities (95% CI: 3.7-4.8); there was a statistically significant difference between the UK and France (P<0.001).

Characteristics of women with PAS

The mean age at delivery, the proportion of obese women and the proportion of women who smoked during pregnancy between the PAS cohorts in the UK and France were not statistically different (Table 2). In women who had PAS and had a previous pregnancy, a statistically significantly higher proportion of women in the UK had at least one previous caesarean section compared to women in France (93% vs. 80%, p=0.003), while a higher proportion of women in France had other previous uterine surgery compared to women in the UK (44% vs. 29%, p=0.007). In both the UK and France, approximately half of women had PAS suspected prior to delivery. There was no statistically significant difference in the grade of PAS between France and the UK; 29% and 22% had a final diagnosis of placenta percreta in the UK and France, respectively.

PAS management

In the UK, over three-quarters of women (76%) had an attempted manual removal of the placenta while this was 68% in France (P<0.001). Women with PAS in the UK were more frequently managed with caesarean hysterectomy than women in France (43% vs. 26%, P<0.001), while a lower proportion of women had their placenta left in situ in the UK compared to France (19% vs. 36%, P<0.001) (Table 3). In women that had a placenta left in situ approach, approximately third of women in the UK and a fifth of women in France went on to have a hysterectomy.

The maternal and infant outcomes of women with PAS

The maternal and infant outcomes are shown in Table 4. The median estimated total blood loss for women with PAS was 3050 millilitres (mLs) (IQR: 1700-6500 mLs) in the UK while it was lower in France with a median of 1000 mls (IQR: 500-2500 mls; P<0.001). Over half of women with PAS in the UK had a severe PPH ≥3000mls while only a fifth of women in France experienced this level of haemorrhage (P<0.001). Among women who had a hysterectomy after an attempted conservative approach, the median blood loss was 2,000 mL (IQR: 500-4000).The difference in blood loss between the UK and France remained consistent when the analysis was restricted to women with placenta percreta, PAS suspected antenatally and in women with placenta praevia detected antenatally (Tables S1-S5).

Approximately three-quarters of women with PAS received a red blood cell (RBC) transfusion in the UK while half of women received an RBC transfusion in France (P<0.001). Nearly two-thirds of women in the UK had a massive blood transfusion compared to half of women with PAS in France (64% vs. 49%, P=0.028). Further information on haematological management is available in Table S6.

In both countries, approximately 20% of women with PAS underwent pelvic arterial embolisation. The UK had a statistically significantly higher proportion of women managed with a uterine balloon tamponade compared to France (25% vs. 15%, P=0.025, respectively). There were similar proportions of women with PAS who had damage to their bowels, urinary tract or bladder. There was no difference in the proportion of women with an infection between the UK and France (2% vs. 1%, p=0.332). ITU admission for women with PAS was higher in UK than for women in France (69% vs. 30%, P<0.001). One woman died, from haemorrhagic shock, which was caused by an attempted manual removal of the placenta and a failed embolisation. In women who had PAS, there was no significant difference in the perinatal mortality between the UK and France.

Discussion

This binational study has shown that management and maternal outcomes were different between the two cohorts of women with PAS in the UK and France despite having similar proportions of placenta percreta and antenatally suspected cases of PAS. In particular, the majority of women with PAS were managed with planned hysterectomy in the UK, while in France, a left in situ approach to conserve the uterus was more commonly attempted. The UK had a larger proportion of women who had a severe postpartum haemorrhage. The difference in severe postpartum haemorrhage between the UK and France remained when the analysis was restricting to women who had antenatal suspicion of PAS, detected placenta praevia and in those who had placenta percreta.

Interpretation

Similar to previous findings, this study showed that the primary management for PAS in the UK was peripartum hysterectomy.[3, 24] A smaller and older case series showed that conservative management of PAS in France was used in 25% of affected women,[17] while the findings from this study showed this approach is now used in half of women with PAS in France.

It is surprising that an attempted manual removal of the placenta occurred in women with an antenatal suspicion of PAS. Nevertheless, this occurred in a large proportion of women in both countries. These findings suggest that clinicians in the UK and France did not adhere to the clinical guidelines of not attempting a manual removal of the placenta and leaving the placenta undisturbed when PAS is suspected.[16, 31, 32] These data indicate that implementation of guidelines needs to be strengthened and women should be referred to tertiary centres with multidisciplinary teams experienced in PAS if there is suspicion of PAS.[32]

Previous studies have shown women had preserved future fertility and reduced haemorrhage risk when PAS was managed conservatively.[15, 21] However, these studies were not population-based and lacked an appropriate comparison group.[17, 33, 34] Greater use of a conservative approach in

France may be a potential explanation for the lower blood loss observed in women with PAS compared to the UK.

Assuming that the complexity of surgery is the same for women in France and the UK, the lack of centralisation of care of PAS in the UK may be a partial explanation for the higher proportion of women with severe postpartum haemorrhage where the UK primarily manages PAS with caesarean hysterectomy. In women with PAS, hysterectomies were performed in the majority of centres in the UK at the time of data collection for this study. A recent study in the UK found that one third of maternity centers in the last five years managed less than one case of PAS per year.[35] In contrast, PAS care was centralised into specialist centers in France; thus, the clinical teams in France were more experienced in managing women with PAS than clinical teams in the UK. Ruiz, Chen [36] showed there was a higher complication, transfusion and mortality rate for hysterectomies performed by inexperienced surgeons compared to experienced surgeons.[36] Furthermore, maternal outcomes improve within the same center as clinical teams become more experienced in managing PAS.[37] Colleagues have shown that women who had modified radical peripartum caesarean hysterectomy conducted by highly skilled and experienced surgical teams had better outcomes compared to normal surgical approaches; accordingly, the experience and skillset of the surgical team matters.[38] In addition, obstetricians and radiologists perform the majority of antenatal imaging in France while a midwife or sonographer performs these scans in the UK. This may have led to varying levels of confidence in the PAS diagnosis between France and the UK, where a manual attempted removal of the placenta was performed more readily in the UK compared to France. Thus, a potential explanation for the difference in blood loss may be the result of differences in the health care system. Although planned, the UK health system has yet to centralise PAS management into multidisciplinary teams that regularly perform complex surgeries for PAS. The results of this study recommend the immediate implementation of these plans in the UK. Other countries should consider centralising PAS care.

Conversely, lower rates of haemorrhage in France in women who had a conservative approach has biological plausibility. After delivery, the blood flow to the uterus will decrease, which will result in necrosis of the placenta and either expulsion or re-absorption of the placenta. Without a rupture, a failed conservative management or trauma to the uterus, there is less likely to be a spontaneous haemorrhage,[18] while even a planned hysterectomy for a placenta percreta is likely to result in major blood loss. Yet, a conservative approach is only possible where postpartum follow-up is feasible as one-fifth of women in France with conservative management had a delayed hysterectomy, and these women had severe blood loss. Future studies are required to compare those with a planned hysterectomy to those with planned conservative management..

Limitations & Strengths

Both the UK and French studies had different case definitions so even with considerable effort to harmonise the definitions of the two studies it was possible that the populations were slightly different. It may be that the UK study was comprised of more severe cases of PAS compared to the French study, which could be a potential explanation for the differences in incidence. Future studies should adopt the same definition or be designed together in a single prospective study, to allow more straightforward comparison. However, despite this limitation, when the analysis was restricted to women with placenta percreta there was still a difference in the estimated blood loss between the two countries. Studies have highlighted issues with sub-classifying PAS; as a result, future prospective studies should use the FIGO guidelines and current evidence to allow for accurate sub-classification, harmonisation and comparability.[39 40]

A randomised controlled trial is the most robust method to examine the causal effect of management on outcome but this would be difficult to conduct in this clinical scenario. In addition, future studies could be further strengthened by including women's satisfaction with care as an outcome or other patient centered outcomes.

Another limitation to note is the management of PAS has changed since these data were collected.[32] Although the UK and French studies were conducted during a comparable time period allowing appropriate comparison, the evolution of knowledge, awareness and management of PAS

across this time period may be a partial explanation for the differences in outcomes between the countries.[41] It should be noted that the data from these two studies may not reflect current practice, yet these data illustrate that differences in health systems affected outcomes for women with PAS.

Conclusion

This binational study showed a substantial difference in blood loss between France and the UK. This may be the result of differences in management or the structure of the health care system. Importantly, the centralisation of care into specialist centers with skilled multidisciplinary teams is required to optimise outcomes for women with PAS. Uterine preserving management may have resulted in a greater number of women retaining their potential fertility and reduced the likelihood of a life-threatening haemorrhagic event. However, if the conservative management approach fails, it is likely to result in severe maternal morbidity, which reinforces recommendations for regular close monitoring of these women.

Contributions

GK, CDT, MK and SM contributed to the conceptualization and investigation. GK was the scientific lead for the PACCRETA study. MK was the scientific lead for the UKOSS study. GK and MK were the data curators. SM completed the formal analysis and wrote the first draft. AS and RR validated the data analysis. GK, CDT, MK, SM, SC, JK and LS provided methodological input into the study. All authors reviewed and edited the manuscript.

Ethical approval

PACCRETA study: The Committee for the Protection of Patients (AOR12156), the Consultative Committee on the Treatment of Personal Health Data for Research Purposes, and the National Data Protection Authority (CNIL n° DR-2013-427) approved the study protocol.

UKOSS: UKOSS methodology has been approved by the London Multi-centre Research Ethics Committee (MREC) (MREC reference 04/MRE02/45).

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Data Sharing Statement

Request for access to the data should be directed to the steering committee of the relevant country. Requests for access to the French data (PACCRETA) should be directed to epope@inserm.fr. Requests for access to the UK dataset will be considered by the National Perinatal Epidemiology Unit Data Sharing committee. Access to the UK data can be requested from general@npeu.ox.ac.uk.

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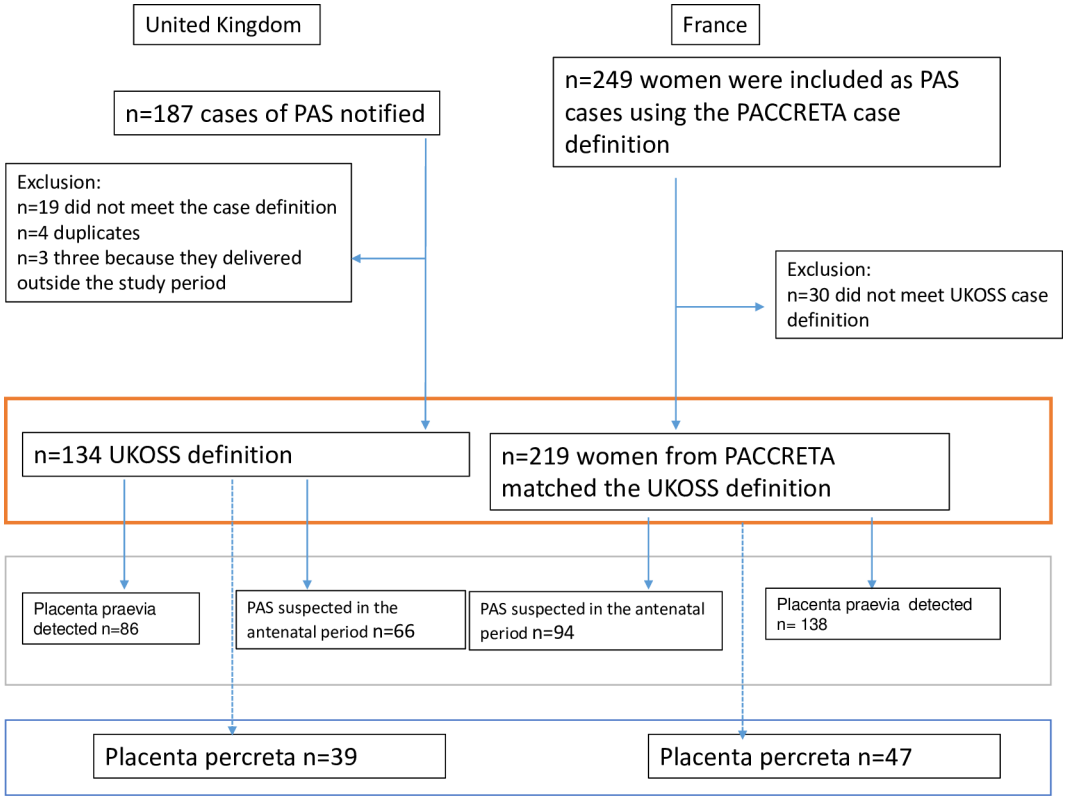
United Kingdom
France
n=187 cases of PAS notified
n=249 women were included as PAS cases using the PACCRETA case definition
Exclusion:
n=19 did not meet the case definition
n=4 duplicates
n=3 three because they delivered outside the study period
Exclusion:
n=30 did not meet UKOSS case definition
n=134 UKOSS definition
n=219 women from PACCRETA matched the UKOSS definition
Placenta praevia detected n=86
PAS suspected in the antenatal period n=66
PAS suspected in the antenatal period n=94
Placenta praevia detected n= 138
Placenta percreta n=39
Placenta percreta n=47

Supplementary methods section

Case selection

A harmonised case definition was selected using the cases from the PACCRETA study that met the stricter UKOSS definition (**Error! Reference source not found.**). The UKOSS definition did not include women who had a haemorrhage as a result of a manual removal of placenta; therefore, there were 16 women from notified UKOSS cases that did not meet the case definition (27). In those who only met the fourth criteria of the PACCRETA study (antenatal diagnosis and at laparotomy), their PACCRETA forms were checked to assess if they met the UKOSS definition. These cases were included if they had a placenta percreta or surgical management for haemorrhage which included a hysterectomy and conservative surgical management.

Comparability of datasets

The PACCRETA data collection form was translated into English, and all data items in the UKOSS data collection form were mapped to the PACCRETA data collection form. The characteristics, management and outcomes of interest were identified from the literature, and if these were available and comparable between datasets, they were extracted. For variables where there was not a uniform definition, a common definition was generated. If this was not possible, then the variable was excluded from the analysis.

Table S1. Current pregnancy characteristics of women with PAS suspected in the antenatal period.

		UK n (%) n=66		France n (%) n=94		P-value
Age mean (SD)		34.1	(5.4)	34.7	(4.4)	0.458
BMI (kg/m^2)	<25	30	(46.2)	42	(46.2)	0.169
	≥25 & <30	23	(35.4)	22	(24.2)	
	≥30	12	(18.5)	27	(29.7)	
	Missing	1		3		
Smoking status	Did not smoke during pregnancy	49	(75.4)	74	(83.1)	0.235
	Smoked during pregnancy	16	(24.6)	15	(16.9)	
	Missing	1		5		
Country of birth	Not France	-	-	46	(52.9)	
	France	-	-	41	(47.1)	
	Missing	-	-	7	-	
Ethnicity	White	51	(77.3)	-	-	
	Non-white	15	(22.7)	-	-	
	Missing	0		-		
Parity	Zero	1	(1.5)	4	(4.3)	0.634
	1	16	(24.2)	25	(26.6)	
	2+	49	(74.2)	65	(69.1)	
History of PPH	No	58	(89.2)	74	(82.2)	0.226
	Yes	7	(10.8)	16	(17.8)	
	N/A (nulliparous)	1		4		
Previous caesarean section	Zero	0	(0)	4	(4.4)	0.308
	1	30	(46.2)	37	(41.1)	
	2+	35	(53.8)	49	(54.4)	
	N/A (nulliparous)	1		4		
Previous uterine surgery	No	50	(75.8)	57	(60.6)	0.045
	Yes	16	(24.2)	37	(39.4)	
	Missing	0		0		
Previous uterine surgery and caesarean section	Yes	66	(100)	94	(100)	-
Hypertensive disorder during pregnancy	Yes	0	(0.0)	5	(5.3)	0.079
	Missing	1		0		
Placenta praevia detected prior to delivery	Yes	64	(97.0)	86	(91.5)	0.159
	Missing	0		0		
Multiple pregnancy	Yes	0	(0.0)	1	(1.1)	0.999
PAS type	Placenta accreta/ increta	42	(64.6)	53	(56.4)	0.298
	Placenta percreta	23	(35.4)	41	(43.6)	
	Missing	1		0		

Descriptive statistics calculated excluding the missing.

Table S2. Obstetric and haematological management of women with PAS suspected in the antenatal period.

		Abnormally invasive placenta suspected in antenatal period				
Delivery and management		UK n(%) n=66		France n(%) n=94		P-value
Termination of pregnancy	Yes	0	(0.0)	1	(1.1)	0.999
Gestational age at birth	<34 weeks	12	(18.2)	19	(20.2)	0.044
	≥34 & <37 weeks	25	(37.9)	51	(54.3)	
	≥37 weeks	29	(43.9)	24	(25.5)	
Planned caesarean section	Yes	64	(97.0)	85	(90.4)	0.107
Caesarean section	Yes	65	(98.5)	94	(100)	0.231
Medical management						
Uterotonics used as treatment or prophylaxis*	Used	52	(78.8)	59	(63.4)	0.038
	Missing	0		1		
Attempt to manually remove the placenta	*Attempt*	39	(59.1)	26	(28.0)	<0.001
	No attempt	27	(40.9)	67	(72.0)	
	Missing	0		1		
Caesarean Hysterectomy	Yes	34	(51.5)	28	(29.8)	0.005
	No	32	(48.5)	66	(70.2)	
Total Hysterectomy	Yes	43	(65.2)	45	(47.9)	0.031
	No	23	(34.8)	49	(52.1)	
Hysterectomy planned	Yes	32	(74.4)	7	(15.6)	<0.001
	No	11	(25.6)	38	(84.4)	
Time between birth and hysterectomy	≤48hrs	40	(93.0)	34	(75.6)	0.025
	>48hrs	3	(7.0)	11	(24.4)	
Conservative approach: placenta left in situ	Yes	18	(27.3)	53	(56.4)	<0.001
	No	48	(72.7)	41	(43.6)	
How much left in situ	Complete	14	(77.8)	39	(73.6)	0.724
	Partial	4	(22.2)	14	(26.4)	
Hysterectomy after left in situ	*Yes*	4	(22.2)	17	(32.1)	0.429
Time between birth and hysterectomy	<48hrs	1	(25.0)	6	(35.3)	0.999
	>48hrs	3	(75.0)	11	(64.7)	
Methotrexate used	*Yes*	5	(27.8)	0	(0)	0.001
Pelvic arterial embolisation	Used	30	(45.5)	33	(35.1)	0.187
Other conservative surgery*	Used	13	(19.7)	9	(9.6)	0.067
Uterine balloon tamponade	Used	10	(15.2)	6	(6.4)	0.069
Haematological management						
Whole blood or Red blood cells received n(%)		45	(68.2)	47	(50.0)	0.022
In women who received whole blood or Red blood cells	median (IQR) unit	7	(4-10)	5	(3-10)	0.309
FFP received n(%)		33	(50.0)	33	(35.1)	0.060
In women who received FFP	median (IQR) unit	4	(3-6)	5	(2-8)	0.342
Platelets received n(%)		19	(28.8)	10	(10.6)	0.003
In women who received platelets	median (IQR) unit	2	(1-4)	2	(1-4)	0.864
Fibrinogen received e.g cryoprecipitate or fibrinogen conc.	Yes	15	(22.7)	27	(28.7)	0.396
Recombinant Factor VIIa used	Yes	1	(1.5)	1	(1.1)	0.999

*Includes: arterial ligation and uterine compression sutures. Descriptive statistics calculated excluding the missing.

Table S3. Maternal and infant outcomes of women with PAS suspected in the antenatal period.

		Abnormally invasive placenta suspected in antenatal period				
Maternal outcomes		UK n(%) n=66		France n(%) n=94		P-value
Amount of blood loss (mL)	Median (IQR)	3000	(1000-6500)	925	(500-2000)	<0.001
Severe postpartum haemorrhage (mL)	<3000	32	(48.5)	74	(82.2)	<0.001
	≥3000	34	(51.5)	16	(17.8)	
	Missing	0		4		
Postpartum haemorrhage (mL)	<2000	25	(37.9)	66	(73.3)	<0.001
	≥2000	41	(62.1)	24	(26.7)	
	Missing	0		4		
Massive Transfusion (units)	≥6	30	(66.7)	21	(45.7)	0.043
	<6	15	(33.3)	25	(54.3)	
	Missing	0		1		
Postpartum infection	Yes	0	(0.0)	2	(2.1)	0.233
Damage to bowel, urinary tract and bladder	Yes	8	(12.1)	11	(11.7)	0.936
	Missing	0		0		
ITU admission	Yes	53	(80.3)	37	(39.4)	<0.001
	Missing	0		0		
Maternal mortality	Yes	0	(0.0)	1	(1.1)	0.999
Infant outcomes		UK n (%) n=66		France n (%) n=95		
Perinatal mortality	*No*	65	(98.5)	94	(98.9)	0.999
	Yes	1	(1.5)	1	(1.1)	
	Missing	0		0		

Descriptive statistics calculated excluding the missing.

Table S4. Management and maternal and infant outcomes of women with placenta percreta.

Management		UK n(%) n=39		France n(%) n=47		P-Value
PAS suspected prior to delivery	Yes	23	(59)	42	(89.4)	0.001
	No	16	(41)	5	(10.6)	
Caesarean section	Yes	36	(92.3)	47	(100)	0.089
Caesarean Hysterectomy	Yes	19	(48.7)	18	(38.3)	0.331
	No	20	(51.3)	29	(61.7)	
Total Hysterectomy	Yes	24	(61.5)	30	(63.8)	0.827
	No	15	(38.5)	17	(36.2)	
Time between delivery and total hysterectomy	≤48hrs	21	(87.5)	23	(76.7)	0.309
	>48hrs	3	(12.5)	7	(23.3)	
	Attempt	19	(48.7)	8	(17.4)	0.002
	No attempt	20	(51.3)	38	(82.6)	
No attempt to remove placenta after birth	Missing	0		1		
	Yes	13	(33.3)	29	(61.7)	0.009
Conservative approach: placenta left in situ	No	26	(66.7)	18	(38.3)	
	Unknown	0		0		
How much left in situ	Complete	11	(84.6)	23	(79.3)	0.686
	Partial	2	(15.4)	6	(20.7)	
Had hysterectomy after left in situ	*Yes*	4	(30.8)	12	(41.4)	0.513
Time between birth and hysterectomy	≤48hrs	1	(25.0)	5	(41.7)	0.999
	>48hrs	3	(75.0)	7	(58.3)	
Methotrexate used	*Yes*	5	(38.5)	0	(0)	0.002
Pelvic arterial embolisation	Not used	25	(64.1)	27	(57.4)	0.530
	Used	14	(35.9)	20	(42.6)	
Other conservative surgery*	Not used	28	(71.8)	42	(89.4)	0.037
	Used	11	(28.2)	5	(10.6)	
Whole blood or Red blood cells received n(%)		28	(71.8)	30	(63.8)	0.433
In women who received whole blood or Red blood cells	median (IQR) unit	8	(6-14)	6	(3-11)	0.203
FFP received n(%)		20	(51.3)	26	(55.3)	0.709
In women who received FFP	median (IQR) units	4	(4-8)	4	(2-8)	0.383
Platelets received n(%)		13	(33.3)	7	(14.9)	0.044
In women who received platelets	median (IQR) units	2	(1-2)	2	(1-8)	0.382
Fibrinogen received e.g cryoprecipitate or fibrinogen conc.	Not used	29	(74.4)	30	(63.8)	0.295
	Used	10	(25.6)	17	(36.2)	
Maternal mortality	Yes	0	(0)	1	(2.1)	0.999
Amount of blood loss (mL)	Median (IQR)	3000	(1500-9000)	1200	(500-3100)	<0.001
Severe postpartum haemorrhage	<3000	18	(46.2)	32	(71.1)	0.020
	≥3000	21	(53.8)	13	(28.9)	
	Missing	0		2		
Postpartum haemorrhage	<2000	12	(30.8)	29	(64.4)	0.002
	≥2000	27	(69.2)	16	(35.6)	
	Missing	0		2		
Massive transfusion	≥ 6	21	(75.0)	16	(55.2)	0.117
	< 6	7	(25.0)	13	(44.8)	
	Missing	0		1		
Postpartum infection	Yes	0	(0.0)	7	(14.9)	0.015
Damage to bowel, urinary tract and bladder	Yes	6	(15.4)	8	(17)	0.838
ITU admission	Yes	31	(79.5)	19	(40.4)	<0.001
Infant outcomes		UK n(%) n=39		France n(%) n=47		
Perinatal mortality	*Yes*	1	(2.8)	1	(2.13)	0.999
	Missing	3		0		

* Includes: arterial ligation and uterine compression sutures. Descriptive statistics calculated excluding the missing.

Table S5. Management and maternal and infant outcomes of women who had antenatally detected placenta praevia.

Management		UK n(%) n=86		France n(%) n=138		P-Value
PAS suspected prior to birth	Yes	64	(74.4)	86	(65.2)	0.149
	No	22	(25.6)	46	(34.8)	
	Missing	0		6		
Caesarean section	Yes	83	(96.5)	132	(95.7)	0.750
	Yes	46	(53.5)	46	(33.3)	0.003
Caesarean hysterectomy	No	40	(46.5)	92	(66.7)	
	Missing	0		0		
Total hysterectomy	Yes	56	(65.1)	66	(48.2)	0.013
	No	30	(34.9)	71	(51.8)	
	Missing	0		1		
Time between birth and hysterectomy	≤48hrs	53	(94.6)	53	(80.3)	0.019
	>48hrs	3	(5.4)	13	(19.7)	
No attempt to remove placenta after birth	Attempt	58	(67.4)	62	(45.3)	0.001
	No attempt	28	(32.6)	75	(54.7)	
	Missing	0		1		
Conservative approach: placenta left in situ	Yes	20	(23.3)	59	(42.8)	0.003
	No	66	(76.7)	79	(57.2)	
	Unknown			2		
How much left in situ	Complete	15	(75.0)	36	(61)	0.259
	Partial	5	(25.0)	23	(39)	
Had hysterectomy after left in situ	Yes	5	(25.0)	18	(30.5)	0.639
Pelvic arterial embolisation	Used	30	(34.9)	39	(28.3)	0.296
Other conservative surgery*	Used	18	(20.9)	23	(16.7)	0.422
Whole blood or Red blood cells received n(%)		64	(74.4)	77	(55.8)	0.005
In women who received whole blood or Red blood cells	median (IQR) unit	7	(4-12)	6	(3-11)	0.373
FFP received n(%)		47	(54.7)	60	(43.5)	0.103
In women who received FFP	median (IQR) units	4	(4-8)	5	(2-8)	
Platelets received n(%)		29	(33.7)	20	(14.5)	0.001
In women who received platelets	median (IQR) units	2	(1-2)	1	(1-2)	
Fibrinogen received	Used	21	(24.4)	48	(34.8)	0.102
Maternal outcomes						
Maternal mortality	Yes	0	(0.0)	1	(0.7)	0.999
Amount of blood loss *(mL)*	Median (IQR)	3000	(1500-7000)	1200	(500-2500)	
Postpartum haemorrhage (mL)	<3000	38	(44.2)	100	(76.3)	<0.001
	≥3000	48	(55.8)	31	(23.7)	
	Missing	0		7		
Severe postpartum haemorrhage (mL)	<2000	25	(29.1)	85	(64.9)	<0.001
	≥2000	61	(70.9)	46	(35.1)	
	Missing	0		7		
Massive transfusion (units)	≥6	43	(67.2)	38	(50.7)	0.049
	< 6	21	(32.8)	37	(49.3)	
	Missing	0		2		
Postpartum infection	Yes	2	(2.3)	3	(2.2)	0.953
Damage to bowel, urinary tract and bladder	Yes	10	(11.6)	15	(11)	0.891
ITU admission	Yes	67	(77.9)	50	(36.5)	<0.001
Infant outcomes		UK n(%) n=86		France n(%) n=138		
Perinatal mortality	*Yes*	2	(2.3)	3	(2.2)	0.999
	Missing	1		3		

* Includes: arterial ligation and uterine compression sutures. Descriptive statistics calculated excluding the missing.

Table S6. Pregnancy characteristics and haematological management of women with PAS

Pregnancy characteristics		**UK n(%) n=134**		**France n(%) n=219**		P-value
Termination of pregnancy	Yes	2	(1.5)	1	(0.5)	0.559
	Missing	2		0		
Gestational age at birth	<34 weeks	23	(17.2)	39	(17.8)	0.874
	≥34 & <37 weeks	43	(32.1)	75	(34.2)	
	≥37 weeks	68	(50.7)	105	(47.9)	
Planned caesarean section	Yes	110	(83.3)	138	(63.0)	<0.001
	Missing	2		0		
Haematological management						
FFP received n (%)		69	(51.5)	88	(40.2)	0.038
In women who received FFP	median (IQR) units	4	(4-7)	4	(2-8)	0.716
Platelets received n (%)		43	(32.1)	29	(13.2)	<0.001
In women who received platelets	median (IQR) units	2	(1-2)	1	(1-4)	0.859
Fibrinogen received e.g. cryoprecipitate or fibrinogen conc.	Yes	34	(25.4)	69	(31.5)	0.219
Recombinant Factor VIIa used	Yes	5	(3.7)	3	(1.4)	0.148

Descriptive statistics calculated excluding the missing.

Table 1. Case definitions from the respective studies.

UKOSS study case definition	**PACCRETA study case definition**
Women were included as having PAS if they met either of the following criteria: **1.** Placenta accreta/increta/percreta diagnosed histologically following hysterectomy or post-mortem. **Or** **2.** An abnormally adherent placenta, **requiring active management**, including conservative approaches where the placenta is left in situ. **Excluded** women who had a manual placental removal with minimal or moderate difficulty but required no additional active management. **Active management:** this is when some other manipulation is required to remove the placenta and the placenta can only be partially removed or is removed piecemeal with clear documentation that the clinician did not feel it was fully removed.	Women were included as having PAS if they met any of the following criteria: 1) manual removal of the placenta partially or totally impossible and no cleavage plane between part or all of the placenta and the uterus 2) massive bleeding from the implantation site after forced placental removal in the absence of another cause of postpartum haemorrhage (PPH) 3) histological confirmation of PAS on a hysterectomy specimen 4) signs of PAS at laparotomy in women with suspected PAS on prenatal imaging.

Harmonised definition for comparative study

Women were included as having abnormally invasive placenta if they met either of the following criteria:

1. Placenta accreta/increta/percreta diagnosed histologically following hysterectomy or post-mortem.

Or

2. An abnormally adherent placenta, **requiring active management**, including conservative approaches where the placenta is left in situ.

Active management was the same as the UKOSS case definition.

Exclusion: Women who had a difficult manual removal of the placenta but did not require active management were excluded from the study as there was no evidence to confirm PAS.

Table 2. Characteristics of women with PAS in the UK and France

		UK n(%) n=134		France n(%) n=219		P-value
Age Mean (SD)		34.6	(5.6)	34.5	(5.1)	0.833
BMI (kg/m^2)	<25	60	(45.8)	119	(55.3)	0.111
	≤25-<30	42	(32.1)	48	(22.3)	
	≥30	29	(22.1)	48	(22.3)	
	Missing	3		4		
Smoking Status	Did not smoke during pregnancy	107	(80.5)	165	(78.6)	0.675
	Smoked during pregnancy	26	(19.5)	45	(21.4)	
	Missing	1		9		
Country of birth	Not France	-	-	87	(42.4)	
	France	-	-	118	(57.6)	
	Missing	-	-	14		
Ethnicity	White	99	(74.4)	-	-	
	Non-white	34	(26.6)	-	-	
	Missing	1		-	-	
Parity	Zero	12	(9)	37	(16.9)	0.082
	1	39	(29.1)	66	(30.1)	
	2+	83	(61.9)	116	(53.0)	
History of PPH	No	111	(91)	145	(79.7)	0.008
	Yes	11	(9)	37	(20.3)	
	N/A (nulliparous)	12		37		
Previous caesarean section	Zero	9	(7.4)	36	(19.8)	0.011
	1	63	(51.6)	80	(44)	
	2+	50	(41.0)	66	(36.3)	
	N/A (nulliparous)	12		37		
*Previous uterine surgery**	No	94	(70.7)	123	(56.2)	0.007
	Yes	39	(29.3)	96	(43.8)	
	Missing	1		0		
Previous uterine surgery and caesarean section	Yes	129	(96.3)	207	(94.5)	0.457
Hypertensive disorder during pregnancy	Yes	6	(4.6)	20	(9.1)	0.116
	Missing	3		0		
Placenta praevia detected prior to birth	Yes	86	(64.7)	138	(63.0)	0.755
	Missing	1		0		
Multiple pregnancy	Yes	4	(3.0)	10	(4.6)	0.460
PAS suspected prior to birth	Yes	66	(49.6)	94	(44.8)	0.379
	Missing	1		9		
PAS type	Placenta accreta/ increta	94	(70.7)	172	(78.5)	0.096
	Placenta percreta	39	(29.3)	47	(21.5)	
	Missing	1		0		

*Includes myomectomy, cavity breached, dilation & curettage, previous surgical termination of pregnancy and evacuation of retained products of conception (excludes caesarean section). Descriptive statistics calculated excluding the missing. BMI: Body Mass Index; PAS: placenta accreta spectrum; PPH: postpartum haemorrhage.

Table 3. Mode of birth and management of women with PAS in the UK and France

Management		UK n(%) n=134		France n(%) n=219		P-value
Caesarean section	Yes	118	(88.1)	187	(85.4)	0.477
Uterotonics used as treatment or prophylaxis*	Used	109	(81.3)	164	(75.2)	0.182
	Missing	0		1		
Attempt to manually remove the placenta	Attempt	102	(76.1)	149	(68.3)	<0.001
	No attempt	32	(23.9)	69	(31.7)	
	Missing	0		1		
In women with antenatal care suspicion of AIP: attempt to manually remove the placenta	*Attempt*	39	(59.1)	26	(28.0)	<0.001
	No attempt	27	(40.9)	67	(72.0)	
	Missing	0		1		
Caesarean hysterectomy**	Yes	58	(43.3)	57	(26.0)	<0.001
	No	76	(56.7)	162	(74.0)	
Total hysterectomy	Yes	79	(59.0)	83	(38.1)	<0.001
	No	55	(41.0)	135	(61.9)	
	Missing	0		1		
Hysterectomy planned	Yes	38	(48.1)	9	(10.8)	<0.001
	No	41	(51.9)	74	(89.2)	
Time between birth and hysterectomy	≤48hrs	73	(92.4)	70	(84.3)	0.111
	>48hrs	6	(7.6)	13	(15.7)	
Conservative approach: placenta left in situ***	Yes	26	(19.4)	79	(36.1)	<0.001
	No	108	(80.6)	140	(63.9)	
How much left in situ	Complete	18	(69.2)	40	(50.6)	0.098
	Partial	8	(30.8)	39	(49.4)	
Hysterectomy after left in situ	*Yes*	8	(30.8)	18	(22.8)	0.413
Time between birth and hysterectomy	≤48hrs	3	(37.5)	7	(38.9)	0.946
	>48hrs	5	(62.5)	11	(61.1)	
Methotrexate used	*Yes*	7	(26.9)	0	(0.0)	<0.001
	Missing	0		1		

*Use of misoprostol, ergometrine, syntocinon, sulprostone or other prostaglandin. Descriptive statistics calculated excluding the missing. **Caesarean hysterectomy was defined as women who had a hysterectomy within 4 hours of caesarean section in the UK; for the French data, caesarean hysterectomy was indicated in the operative record.
*** Conservative approach was verified from the medical notes in France; for the UK data this was derived as women who had placenta left in situ without caesarean hysterectomy.

Table 4. Maternal and infant outcomes in women with PAS in the UK and France

Maternal outcomes		UK n(%) n=134		France n(%) n=219		P-value
Total blood loss (mL)	Median (IQR)	3050	(1700-6500)	1000	(500-2500)	<0.001
Severe postpartum haemorrhage (mL)	<3000	57	(42.5)	165	(79.3)	<0.001
	≥3000	77	(57.5)	43	(20.6)	
	Missing	0		11		
Postpartum haemorrhage (mL)	<2000	37	(27.6)	143	(68.8)	<0.001
	≥2000	97	(72.4)	65	(31.1)	
	Missing	0		11		
Whole blood or Red blood cells received n(%)		102	(76.1)	111	(50.7)	<0.001
In women who received whole blood or Red blood cells	median (IQR) unit	7	(4-12)	5	(3-10)	0.135
Massive transfusion (units)	≥6	65	(63.7)	52	(48.6)	0.028
	<6	37	(36.3)	55	(51.4)	
	Missing	0		4		
Pelvic arterial embolisation	Used	33	(24.6)	49	(22.4)	0.627
Other conservative surgery for haemorrhage*	Used	28	(20.9)	31	(14.2)	0.100
Uterine balloon tamponade	Used	33	(24.6)	33	(15.1)	0.025
Postpartum infection **	Yes	3	(2.2)	3	(1.4)	0.332
	Missing	0		3		
Damage to bowel, urinary tract and bladder	Yes	10	(7.5)	17	(7.9)	0.889
	Missing	0		3		
ITU admission	Yes	92	(68.7)	65	(30)	<0.001
	Missing	0		2		
Maternal mortality	Yes	0	(100)	1***	(0.5)	0.999
Infant outcomes †		UK n(%) n=138		France n(%) n=229		
Perinatal mortality	*No*	132	(98.5)	222	(98.7)	0.759
	Yes	2	(2.0)	3	(1.3)	
	Missing	4		4		

*Includes: arterial ligation and uterine compression sutures. **UK data were extracted from free text of "did woman have any other morbidity?" and French data were based from specific questions on infective symptoms, haematological culture, symptoms of fever and septic shock. *** The cause of death was haemorrhagic shock, and the secondary factors that led to death were an attempted manual removal of the placenta and a failed embolisation †The denominator is the number of infants. Descriptive statistics calculated excluding the missing.

Title: Placenta accreta spectrum - variations in clinical practice and maternal morbidity between UK and France: a population-based comparative study

Running title: Variation in management of placenta accreta spectrum between UK and France.

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Abstract. (Words: 250/250)

Objective: To compare the management and outcomes of women with Placenta Accreta Spectrum (PAS) in France and the UK.

Design: Two population-based cohorts.

Setting: All obstetrician-led hospitals in the UK and maternity hospitals in eight French regions.

Population: Two-hundred and nineteen women with PAS in France and one-hundred and thirty-four women in the UK.

Methods: The management and outcomes of women with PAS were compared between the UK and France.

Main outcome measures: Median blood loss, severe postpartum haemorrhage (≥3 litres), postpartum infection and damage to surrounding organs.

Results: The management differed between the two countries; a larger proportion of women with PAS in UK had a caesarean hysterectomy compared to France (43% vs. 26%, P<0.001), while in France, a larger proportion of women with PAS had a uterus conserving approach compared to the UK (36% vs. 19%, <0.001). The 24-hour median blood loss in the UK was 3 litres (IQR:1.7-6.5) compared to 1 litre (IQR:0.5-2.5) in France; more women in the UK had a severe PPH compared to women with PAS in France (58% vs. 21%, P<0.001). There was no difference between the UK and French populations for postpartum infection or organ damage.

Discussion: UK and France have very different approaches to managing PAS, with more women in France receiving a uterine conserving and more women undergoing caesarean hysterectomy in the UK. A life-threatening haemorrhage was more common in the UK than in France, which may be the result of differential management and/or the organisation of healthcare systems.

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Key words: Placenta accreta spectrum, management, haemorrhage, hysterectomy, conservative management

Tweetable abstract: In women with placenta accreta spectrum, severe haemorrhage was more common in UK vs. France.

Introduction

Placenta accreta spectrum (PAS) includes placenta accreta, increta, and percreta and is traditionally characterised histologically by a total or partial absence of decidua and placental adherence to or invasion of the myometrium.[1] PAS becomes a clinical problem after birth when the placenta does not physiologically detach from the uterus and forcible placental removal is followed by massive obstetric haemorrhage (MOH) leading to further morbidity and risk of maternal death.[2-4] PAS incidence has accelerated in recent decades,[5-7] simultaneously with the rise in caesarean section rates, which have surpassed 30% in many high-resource countries.[8-10]

Early detection and a planned management have been associated with improved maternal outcomes. Antenatal detection of PAS is critical to the prevention of maternal morbidity arising from PAS as it[11, 12] enables appropriate management through a multi-disciplinary team within a well-equipped tertiary centre with experience in managing the complexity presented by PAS.[11-14] The management of PAS can be broadly subdivided into two main approaches: conservative approaches or caesarean hysterectomy. However, comparison of these approaches for women with PAS has not been robustly investigated.[15-17]

Caesarean hysterectomy is considered the standard approach to manage PAS[11, 18] and forms the mainstay of the management of PAS by many authorities and clinicians internationally, including in the UK.[3] Previous studies have shown caesarean hysterectomy to be lifesaving treatment for women where other uterus conserving surgeries fail.[19, 20] Others have used an approach to conserve the uterus where the placenta is left in situ either partially or completely without attempted removal.[17, 21] This approach is the most common method of conservative management.[22] Given the rarity, potential severity and heterogeneity in management, a randomized controlled trial would be extremely difficult to perform in this area. Therefore, an international comparison between countries with different management policies of PAS may help to answer whether a conservative approach is effective and safe.

Currently, a uterine conserving approach is frequently used in women with PAS in France. French guidelines propose the two options: treatment to conserve the uterus or caesarean hysterectomy.[23] Conversely, UK guidelines recommend caesarean-hysterectomy as the standard management and leaving the placenta in situ only for women desiring uterine preservation or when the surgical team considers caesarean-hysterectomy inappropriate.[24] This cross-country variation offers an opportunity to study and compare the outcomes from two countries. This study aimed to compare the management and maternal outcomes in women with PAS in France and the UK.

Methods

Study population

This was a binational population-based secondary analysis study of PAS using data from two population-based cohort studies from the UK [25] and France.[26, 27 28] The data were collected nationally in the UK and from eight regions within France. Data were prospectively collected using a national obstetric surveillance system in the UK (UKOSS) and a prospective cohort study in France (PACCRETA).

UKOSS (UK)

The UK data were collected using the UKOSS system and the UKOSS methods have been previously described.[29] In brief, women meeting the case definition were identified nationally in the UK during the period of May 2010 to April 2011. Women with PAS were identified using the case definition in Table 1. Anonymised data were collected using a paper data collection form and a nominated reporter in each maternity hospital in the UK completed this form using the woman's hospital records. The UKOSS data have been published previously.[3, 25]

PACCRETA (France)

The methodology of the PACCRETA study has been described in the published protocol.[26] In summary, this population-based study identified women meeting the case definition (Table 1) during the period of November 2013 to October 2015, from 176 centres across eight regions of France where there were 520,114 maternities, which represents 30% of the national total over the study period. Each centre had a nominated clinician that identified women who met the case definition. In addition, delivery suite logs and electronic records were checked to maximise case ascertainment. Data collected from the medical records of each woman were entered onto a web-based data collection form.[27]

Case definitions

The individual studies' case definitions for France and the UK differed. A common case definition was devised to provide a harmonised dataset of women with PAS, which involved selecting women in France that met the stricter UKOSS definition (Box 1).

Specific classification for variables

Information on comparability of the dataset is available in the supplementary section. The grading of PAS (accreta, increta and percreta) was classified into two categories: placenta percreta and a category containing both placenta increta and accreta, on the basis these are often largely indistinguishable clinically and as some women were treated with a leaving in situ approach with no histological uterine examination when a hysterectomy was avoided. Any history of uterine surgery was combined into a variable that included previous caesarean section, myomectomy, cavity breach, dilation and curettage, previous surgical termination of pregnancy and evacuation of retained products of conception. Uterotonics for treatment of haemorrhage included oxytocin, ergometrine, misoprostol, sulprostone and other synthetic prostaglandins

Management, maternal and infant outcomes

Conservative management was defined as placenta left in situ, either completely or partially in women who did not have a caesarean hysterectomy. Surgical management for haemorrhage included hysterectomy, pelvic arterial embolisation, uterine balloon tamponade and other conservative surgeries included uterine compression sutures and arterial ligation. Hysterectomy was categorised into total hysterectomy (occurring at any point), caesarean hysterectomy (occurring after a caesarean section within 4 hours of birth for the UK women and verified as a caesarean hysterectomy from the operative report for the French women) and hysterectomy after placenta left-in-situ (conservative approach). Planned hysterectomy was indicated in the medical notes if hysterectomy had been planned before delivery. Time of hysterectomy was also available in both datasets.

The outcomes were median estimated total blood loss, severe postpartum haemorrhage (≥3000 millilitres (mls)), major postpartum haemorrhage (≥2000mls), red blood cell (RBC) transfusion, massive blood transfusion (≥6 units of RBC), damage to the bowel, urinary tract or bladder, postpartum infection, Intensive Therapy Unit (ITU) admission and maternal death [30]. Damage to the urinary tract, bowel or bladder was combined into one category. Postpartum infection and damage to surrounding organs were extracted from free text in response to the question of "did woman have any other morbidity?" in the UK and the French data were based on specific questions. The primary infant outcome was perinatal death.

Missing data

Women in France who did not have a postpartum haemorrhage did not have a blood loss value entered; the estimated blood loss for French women without a PPH was imputed to be 500mls, as above this threshold, a PPH would have been recorded in the data collection form.[23] In addition, this avoided possible bias towards French management.

Statistical analysis

Between country analysis

The incidence of PAS was calculated per 10,000 maternities according to the estimated number of maternities (UK), and the reported number of maternities from each maternity unit in France, which occurred during the study period. The confidence intervals were estimated using the exact binomial distribution.

A comparative analysis was undertaken in women who had PAS in both France and the UK. The women's characteristics, medical history, obstetric and haematological management and perinatal and maternal outcomes were compared between France and the UK. Normality was assessed using histograms. Normally distributed continuous variables were presented as means with standard deviations and skewed continuous variables were presented as medians with interquartile ranges. The following statistical tests were used where appropriate: student's t-test, Wilcoxon rank-sum

test, Kruskal-Wallis test, and chi-square tests or the Fisher's exact test. A p-value <0.05 was used to determine statistical significance.

Sensitivity analyses were undertaken to assess results in sub-populations, which included women who had placenta percreta, PAS suspected antenatally, and women with placenta praevia detected antenatally. All statistical analyses were conducted using STATA version 15.1 (Stata Corp LLC, College Station, TX, USA).

Patient and public involvement

The patients and public were involved in the design and interpretation of the UKOSS placenta accreta study as part of the UKOSS Steering Committee. There was no patient and public involvement in the PACCRETA study.

Results

The derived study population in the UK and France is shown in Figure 1. In the UK, there were 134 women with PAS who met the case definition during the period May 2010 to April 2011, in 798,634 maternities. This gave an estimated incidence of PAS in 1.7 women per 10,000 maternities (95%CI: 1.4-2.0). After harmonisation of definitions, 219 women in the PACCRETA study met the same case definition over a two-year period in 2013-2015, among 520,114 maternities. This gave an estimated incidence of PAS of 4.2 women per 10,000 maternities (95% CI: 3.7-4.8); there was a statistically significant difference between the UK and France (P<0.001).

Characteristics of women with PAS

The mean age at delivery, the proportion of obese women and the proportion of women who smoked during pregnancy between the PAS cohorts in the UK and France were not statistically different (Table 2). In women who had PAS and had a previous pregnancy, a statistically significantly higher proportion of women in the UK had at least one previous caesarean section compared to women in France (93% vs. 80%, p=0.003), while a higher proportion of women in France had other previous uterine surgery compared to women in the UK (44% vs. 29%, p=0.007). In both the UK and France, approximately half of women had PAS suspected prior to delivery. There was no statistically significant difference in the grade of PAS between France and the UK; 29% and 22% had a final diagnosis of placenta percreta in the UK and France, respectively.

PAS management

In the UK, over three-quarters of women (76%) had an attempted manual removal of the placenta while this was 68% in France (P<0.001). Women with PAS in the UK were more frequently managed with caesarean hysterectomy than women in France (43% vs. 26%, P<0.001), while a lower proportion of women had their placenta left in situ in the UK compared to France (19% vs. 36%, P<0.001) (Table 3). In women that had a placenta left in situ approach, approximately third of women in the UK and a fifth of women in France went on to have a hysterectomy.

The maternal and infant outcomes of women with PAS

The maternal and infant outcomes are shown in Table 4. The median estimated total blood loss for women with PAS was 3050 millilitres (mLs) (IQR: 1700-6500 mLs) in the UK while it was lower in France with a median of 1000 mls (IQR: 500-2500 mls; P<0.001). Over half of women with PAS in the UK had a severe PPH ≥3000mls while only a fifth of women in France experienced this level of haemorrhage (P<0.001). Among women who had a hysterectomy after an attempted conservative approach, the median blood loss was 2,000 mL (IQR: 500-4000).The difference in blood loss between the UK and France remained consistent when the analysis was restricted to women with placenta percreta, PAS suspected antenatally and in women with placenta praevia detected antenatally (Tables S1-S5).

Approximately three-quarters of women with PAS received a red blood cell (RBC) transfusion in the UK while half of women received an RBC transfusion in France (P<0.001). Nearly two-thirds of women in the UK had a massive blood transfusion compared to half of women with PAS in France (64% vs. 49%, P=0.028). Further information on haematological management is available in Table S6.

In both countries, approximately 20% of women with PAS underwent pelvic arterial embolisation. The UK had a statistically significantly higher proportion of women managed with a uterine balloon tamponade compared to France (25% vs. 15%, P=0.025, respectively). There were similar proportions of women with PAS who had damage to their bowels, urinary tract or bladder. There was no difference in the proportion of women with an infection between the UK and France (2% vs. 1%, p=0.332). ITU admission for women with PAS was higher in UK than for women in France (69% vs. 30%, P<0.001). One woman died, from haemorrhagic shock, which was caused by an attempted manual removal of the placenta and a failed embolisation. In women who had PAS, there was no significant difference in the perinatal mortality between the UK and France.

Discussion

This binational study has shown that management and maternal outcomes were different between the two cohorts of women with PAS in the UK and France despite having similar proportions of placenta percreta and antenatally suspected cases of PAS. In particular, the majority of women with PAS were managed with planned hysterectomy in the UK, while in France, a left in situ approach to conserve the uterus was more commonly attempted. The UK had a larger proportion of women who had a severe postpartum haemorrhage. The difference in severe postpartum haemorrhage between the UK and France remained when the analysis was restricting to women who had antenatal suspicion of PAS, detected placenta praevia and in those who had placenta percreta.

Interpretation

Similar to previous findings, this study showed that the primary management for PAS in the UK was peripartum hysterectomy.[3, 24] A smaller and older case series showed that conservative management of PAS in France was used in 25% of affected women,[17] while the findings from this study showed this approach is now used in half of women with PAS in France.

It is surprising that an attempted manual removal of the placenta occurred in women with an antenatal suspicion of PAS. Nevertheless, this occurred in a large proportion of women in both countries. These findings suggest that clinicians in the UK and France did not adhere to the clinical guidelines of not attempting a manual removal of the placenta and leaving the placenta undisturbed when PAS is suspected.[16, 31, 32] These data indicate that implementation of guidelines needs to be strengthened and women should be referred to tertiary centres with multidisciplinary teams experienced in PAS if there is suspicion of PAS.[32]

Previous studies have shown women had preserved future fertility and reduced haemorrhage risk when PAS was managed conservatively.[15, 21] However, these studies were not population-based and lacked an appropriate comparison group.[17, 33, 34] Greater use of a conservative approach in

France may be a potential explanation for the lower blood loss observed in women with PAS compared to the UK.

Assuming that the complexity of surgery is the same for women in France and the UK, the lack of centralisation of care of PAS in the UK may be a partial explanation for the higher proportion of women with severe postpartum haemorrhage where the UK primarily manages PAS with caesarean hysterectomy. In women with PAS, hysterectomies were performed in the majority of centres in the UK at the time of data collection for this study. A recent study in the UK found that one third of maternity centers in the last five years managed less than one case of PAS per year.[35] In contrast, PAS care was centralised into specialist centers in France; thus, the clinical teams in France were more experienced in managing women with PAS than clinical teams in the UK. Ruiz, Chen [36] showed there was a higher complication, transfusion and mortality rate for hysterectomies performed by inexperienced surgeons compared to experienced surgeons.[36] Furthermore, maternal outcomes improve within the same center as clinical teams become more experienced in managing PAS.[37] Colleagues have shown that women who had modified radical peripartum caesarean hysterectomy conducted by highly skilled and experienced surgical teams had better outcomes compared to normal surgical approaches; accordingly, the experience and skillset of the surgical team matters.[38] In addition, obstetricians and radiologists perform the majority of antenatal imaging in France while a midwife or sonographer performs these scans in the UK. This may have led to varying levels of confidence in the PAS diagnosis between France and the UK, where a manual attempted removal of the placenta was performed more readily in the UK compared to France. Thus, a potential explanation for the difference in blood loss may be the result of differences in the health care system. Although planned, the UK health system has yet to centralise PAS management into multidisciplinary teams that regularly perform complex surgeries for PAS. The results of this study recommend the immediate implementation of these plans in the UK. Other countries should consider centralising PAS care.

Conversely, lower rates of haemorrhage in France in women who had a conservative approach has biological plausibility. After delivery, the blood flow to the uterus will decrease, which will result in necrosis of the placenta and either expulsion or re-absorption of the placenta. Without a rupture, a failed conservative management or trauma to the uterus, there is less likely to be a spontaneous haemorrhage,[18] while even a planned hysterectomy for a placenta percreta is likely to result in major blood loss. Yet, a conservative approach is only possible where postpartum follow-up is feasible as one-fifth of women in France with conservative management had a delayed hysterectomy, and these women had severe blood loss. Future studies are required to compare those with a planned hysterectomy to those with planned conservative management..

Limitations & Strengths

Both the UK and French studies had different case definitions so even with considerable effort to harmonise the definitions of the two studies it was possible that the populations were slightly different. It may be that the UK study was comprised of more severe cases of PAS compared to the French study, which could be a potential explanation for the differences in incidence. Future studies should adopt the same definition or be designed together in a single prospective study, to allow more straightforward comparison. However, despite this limitation, when the analysis was restricted to women with placenta percreta there was still a difference in the estimated blood loss between the two countries. Studies have highlighted issues with sub-classifying PAS; as a result, future prospective studies should use the FIGO guidelines and current evidence to allow for accurate sub-classification, harmonisation and comparability.[39 40]

A randomised controlled trial is the most robust method to examine the causal effect of management on outcome but this would be difficult to conduct in this clinical scenario. In addition, future studies could be further strengthened by including women's satisfaction with care as an outcome or other patient centered outcomes.

Another limitation to note is the management of PAS has changed since these data were collected.[32] Although the UK and French studies were conducted during a comparable time period allowing appropriate comparison, the evolution of knowledge, awareness and management of PAS

across this time period may be a partial explanation for the differences in outcomes between the countries.[41] It should be noted that the data from these two studies may not reflect current practice, yet these data illustrate that differences in health systems affected outcomes for women with PAS.

Conclusion

This binational study showed a substantial difference in blood loss between France and the UK. This may be the result of differences in management or the structure of the health care system. Importantly, the centralisation of care into specialist centers with skilled multidisciplinary teams is required to optimise outcomes for women with PAS. Uterine preserving management may have resulted in a greater number of women retaining their potential fertility and reduced the likelihood of a life-threatening haemorrhagic event. However, if the conservative management approach fails, it is likely to result in severe maternal morbidity, which reinforces recommendations for regular close monitoring of these women.

Contributions

GK, CDT, MK and SM contributed to the conceptualization and investigation. GK was the scientific lead for the PACCRETA study. MK was the scientific lead for the UKOSS study. GK and MK were the data curators. SM completed the formal analysis and wrote the first draft. AS and RR validated the data analysis. GK, CDT, MK, SM, SC, JK and LS provided methodological input into the study. All authors reviewed and edited the manuscript.

Ethical approval

PACCRETA study: The Committee for the Protection of Patients (AOR12156), the Consultative Committee on the Treatment of Personal Health Data for Research Purposes, and the National Data Protection Authority (CNIL n° DR-2013-427) approved the study protocol.

UKOSS: UKOSS methodology has been approved by the London Multi-centre Research Ethics Committee (MREC) (MREC reference 04/MRE02/45).

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Data Sharing Statement

Request for access to the data should be directed to the steering committee of the relevant country. Requests for access to the French data (PACCRETA) should be directed to epope@inserm.fr. Requests for access to the UK dataset will be considered by the National Perinatal Epidemiology Unit Data Sharing committee. Access to the UK data can be requested from general@npeu.ox.ac.uk.

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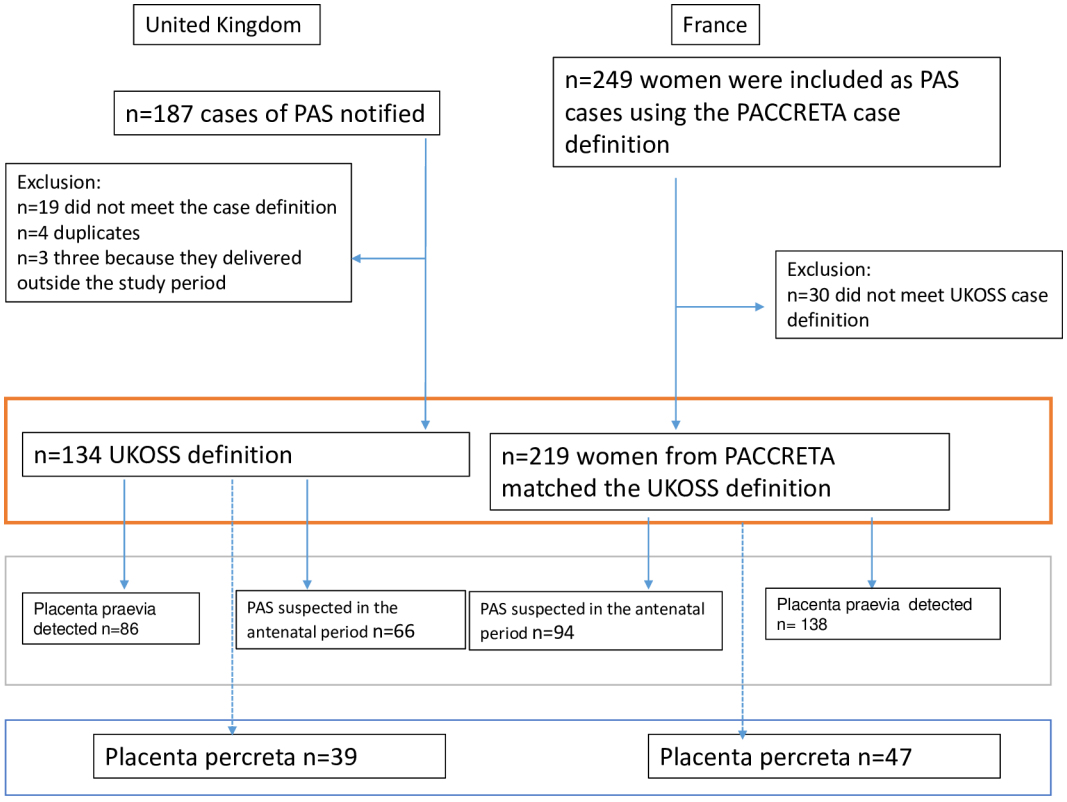
United Kingdom
France
n=187 cases of PAS notified
n=249 women were included as PAS cases using the PACCRETA case definition
Exclusion:
n=19 did not meet the case definition
n=4 duplicates
n=3 three because they delivered outside the study period
Exclusion:
n=30 did not meet UKOSS case definition
n=134 UKOSS definition
n=219 women from PACCRETA matched the UKOSS definition
Placenta praevia detected n=86
PAS suspected in the antenatal period n=66
PAS suspected in the antenatal period n=94
Placenta praevia detected n= 138
Placenta percreta n=39
Placenta percreta n=47

Supplementary methods section

Case selection

A harmonised case definition was selected using the cases from the PACCRETA study that met the stricter UKOSS definition (**Error! Reference source not found.**). The UKOSS definition did not include women who had a haemorrhage as a result of a manual removal of placenta; therefore, there were 16 women from notified UKOSS cases that did not meet the case definition (27). In those who only met the fourth criteria of the PACCRETA study (antenatal diagnosis and at laparotomy), their PACCRETA forms were checked to assess if they met the UKOSS definition. These cases were included if they had a placenta percreta or surgical management for haemorrhage which included a hysterectomy and conservative surgical management.

Comparability of datasets

The PACCRETA data collection form was translated into English, and all data items in the UKOSS data collection form were mapped to the PACCRETA data collection form. The characteristics, management and outcomes of interest were identified from the literature, and if these were available and comparable between datasets, they were extracted. For variables where there was not a uniform definition, a common definition was generated. If this was not possible, then the variable was excluded from the analysis.

Table S1. Current pregnancy characteristics of women with PAS suspected in the antenatal period.

		UK n (%) n=66		France n (%) n=94		P-value
Age mean (SD)		34.1	(5.4)	34.7	(4.4)	0.458
BMI (kg/m^2)	<25	30	(46.2)	42	(46.2)	0.169
	≥25 & <30	23	(35.4)	22	(24.2)	
	≥30	12	(18.5)	27	(29.7)	
	Missing	1		3		
Smoking status	Did not smoke during pregnancy	49	(75.4)	74	(83.1)	0.235
	Smoked during pregnancy	16	(24.6)	15	(16.9)	
	Missing	1		5		
Country of birth	Not France	-	-	46	(52.9)	
	France	-	-	41	(47.1)	
	Missing	-	-	7	-	
Ethnicity	White	51	(77.3)	-	-	
	Non-white	15	(22.7)	-	-	
	Missing	0		-		
Parity	Zero	1	(1.5)	4	(4.3)	0.634
	1	16	(24.2)	25	(26.6)	
	2+	49	(74.2)	65	(69.1)	
History of PPH	No	58	(89.2)	74	(82.2)	0.226
	Yes	7	(10.8)	16	(17.8)	
	N/A (nulliparous)	1		4		
Previous caesarean section	Zero	0	(0)	4	(4.4)	0.308
	1	30	(46.2)	37	(41.1)	
	2+	35	(53.8)	49	(54.4)	
	N/A (nulliparous)	1		4		
Previous uterine surgery	No	50	(75.8)	57	(60.6)	0.045
	Yes	16	(24.2)	37	(39.4)	
	Missing	0		0		
Previous uterine surgery and caesarean section	Yes	66	(100)	94	(100)	-
Hypertensive disorder during pregnancy	Yes	0	(0.0)	5	(5.3)	0.079
	Missing	1		0		
Placenta praevia detected prior to delivery	Yes	64	(97.0)	86	(91.5)	0.159
	Missing	0		0		
Multiple pregnancy	Yes	0	(0.0)	1	(1.1)	0.999
PAS type	Placenta accreta/ increta	42	(64.6)	53	(56.4)	0.298
	Placenta percreta	23	(35.4)	41	(43.6)	
	Missing	1		0		

Descriptive statistics calculated excluding the missing.

Table S2. Obstetric and haematological management of women with PAS suspected in the antenatal period.

		Abnormally invasive placenta suspected in antenatal period				
Delivery and management		UK n(%) n=66		France n(%) n=94		P-value
Termination of pregnancy	Yes	0	(0.0)	1	(1.1)	0.999
Gestational age at birth	<34 weeks	12	(18.2)	19	(20.2)	0.044
	≥34 & <37 weeks	25	(37.9)	51	(54.3)	
	≥37 weeks	29	(43.9)	24	(25.5)	
Planned caesarean section	Yes	64	(97.0)	85	(90.4)	0.107
Caesarean section	Yes	65	(98.5)	94	(100)	0.231
Medical management						
Uterotonics used as treatment or prophylaxis*	Used	52	(78.8)	59	(63.4)	0.038
	Missing	0		1		
Attempt to manually remove the placenta	*Attempt*	39	(59.1)	26	(28.0)	<0.001
	No attempt	27	(40.9)	67	(72.0)	
	Missing	0		1		
Caesarean Hysterectomy	Yes	34	(51.5)	28	(29.8)	0.005
	No	32	(48.5)	66	(70.2)	
Total Hysterectomy	Yes	43	(65.2)	45	(47.9)	0.031
	No	23	(34.8)	49	(52.1)	
Hysterectomy planned	Yes	32	(74.4)	7	(15.6)	<0.001
	No	11	(25.6)	38	(84.4)	
Time between birth and hysterectomy	≤48hrs	40	(93.0)	34	(75.6)	0.025
	>48hrs	3	(7.0)	11	(24.4)	
Conservative approach: placenta left in situ	Yes	18	(27.3)	53	(56.4)	<0.001
	No	48	(72.7)	41	(43.6)	
How much left in situ	Complete	14	(77.8)	39	(73.6)	0.724
	Partial	4	(22.2)	14	(26.4)	
Hysterectomy after left in situ	*Yes*	4	(22.2)	17	(32.1)	0.429
Time between birth and hysterectomy	<48hrs	1	(25.0)	6	(35.3)	0.999
	>48hrs	3	(75.0)	11	(64.7)	
Methotrexate used	*Yes*	5	(27.8)	0	(0)	0.001
Pelvic arterial embolisation	Used	30	(45.5)	33	(35.1)	0.187
Other conservative surgery*	Used	13	(19.7)	9	(9.6)	0.067
Uterine balloon tamponade	Used	10	(15.2)	6	(6.4)	0.069
Haematological management						
Whole blood or Red blood cells received n(%)		45	(68.2)	47	(50.0)	0.022
In women who received whole blood or Red blood cells	median (IQR) unit	7	(4-10)	5	(3-10)	0.309
FFP received n(%)		33	(50.0)	33	(35.1)	0.060
In women who received FFP	median (IQR) unit	4	(3-6)	5	(2-8)	0.342
Platelets received n(%)		19	(28.8)	10	(10.6)	0.003
In women who received platelets	median (IQR) unit	2	(1-4)	2	(1-4)	0.864
Fibrinogen received e.g cryoprecipitate or fibrinogen conc.	Yes	15	(22.7)	27	(28.7)	0.396
Recombinant Factor VIIa used	Yes	1	(1.5)	1	(1.1)	0.999

*Includes: arterial ligation and uterine compression sutures. Descriptive statistics calculated excluding the missing.

Table S3. Maternal and infant outcomes of women with PAS suspected in the antenatal period.

		Abnormally invasive placenta suspected in antenatal period				
Maternal outcomes		UK n(%) n=66		France n(%) n=94		P-value
Amount of blood loss (mL)	Median (IQR)	3000	(1000-6500)	925	(500-2000)	<0.001
Severe postpartum haemorrhage (mL)	<3000	32	(48.5)	74	(82.2)	<0.001
	≥3000	34	(51.5)	16	(17.8)	
	Missing	0		4		
Postpartum haemorrhage (mL)	<2000	25	(37.9)	66	(73.3)	<0.001
	≥2000	41	(62.1)	24	(26.7)	
	Missing	0		4		
Massive Transfusion (units)	≥6	30	(66.7)	21	(45.7)	0.043
	<6	15	(33.3)	25	(54.3)	
	Missing	0		1		
Postpartum infection	Yes	0	(0.0)	2	(2.1)	0.233
Damage to bowel, urinary tract and bladder	Yes	8	(12.1)	11	(11.7)	0.936
	Missing	0		0		
ITU admission	Yes	53	(80.3)	37	(39.4)	<0.001
	Missing	0		0		
Maternal mortality	Yes	0	(0.0)	1	(1.1)	0.999
Infant outcomes		UK n (%) n=66		France n (%) n=95		
Perinatal mortality	*No*	65	(98.5)	94	(98.9)	0.999
	Yes	1	(1.5)	1	(1.1)	
	Missing	0		0		

Descriptive statistics calculated excluding the missing.

Table S4. Management and maternal and infant outcomes of women with placenta percreta.

Management		UK n(%) n=39		France n(%) n=47		P-Value
PAS suspected prior to delivery	Yes	23	(59)	42	(89.4)	0.001
	No	16	(41)	5	(10.6)	
Caesarean section	Yes	36	(92.3)	47	(100)	0.089
Caesarean Hysterectomy	Yes	19	(48.7)	18	(38.3)	0.331
	No	20	(51.3)	29	(61.7)	
Total Hysterectomy	Yes	24	(61.5)	30	(63.8)	0.827
	No	15	(38.5)	17	(36.2)	
Time between delivery and total hysterectomy	≤48hrs	21	(87.5)	23	(76.7)	0.309
	>48hrs	3	(12.5)	7	(23.3)	
	Attempt	19	(48.7)	8	(17.4)	0.002
	No attempt	20	(51.3)	38	(82.6)	
No attempt to remove placenta after birth	Missing	0		1		
	Yes	13	(33.3)	29	(61.7)	0.009
Conservative approach: placenta left in situ	No	26	(66.7)	18	(38.3)	
	Unknown	0		0		
How much left in situ	Complete	11	(84.6)	23	(79.3)	0.686
	Partial	2	(15.4)	6	(20.7)	
Had hysterectomy after left in situ	*Yes*	4	(30.8)	12	(41.4)	0.513
Time between birth and hysterectomy	≤48hrs	1	(25.0)	5	(41.7)	0.999
	>48hrs	3	(75.0)	7	(58.3)	
Methotrexate used	*Yes*	5	(38.5)	0	(0)	0.002
Pelvic arterial embolisation	Not used	25	(64.1)	27	(57.4)	0.530
	Used	14	(35.9)	20	(42.6)	
Other conservative surgery*	Not used	28	(71.8)	42	(89.4)	0.037
	Used	11	(28.2)	5	(10.6)	
Whole blood or Red blood cells received n(%)		28	(71.8)	30	(63.8)	0.433
In women who received whole blood or Red blood cells	median (IQR) unit	8	(6-14)	6	(3-11)	0.203
FFP received n(%)		20	(51.3)	26	(55.3)	0.709
In women who received FFP	median (IQR) units	4	(4-8)	4	(2-8)	0.383
Platelets received n(%)		13	(33.3)	7	(14.9)	0.044
In women who received platelets	median (IQR) units	2	(1-2)	2	(1-8)	0.382
Fibrinogen received e.g cryoprecipitate or fibrinogen conc.	Not used	29	(74.4)	30	(63.8)	0.295
	Used	10	(25.6)	17	(36.2)	
Maternal mortality	Yes	0	(0)	1	(2.1)	0.999
Amount of blood loss (mL)	Median (IQR)	3000	(1500-9000)	1200	(500-3100)	<0.001
Severe postpartum haemorrhage	<3000	18	(46.2)	32	(71.1)	0.020
	≥3000	21	(53.8)	13	(28.9)	
	Missing	0		2		
Postpartum haemorrhage	<2000	12	(30.8)	29	(64.4)	0.002
	≥2000	27	(69.2)	16	(35.6)	
	Missing	0		2		
Massive transfusion	≥ 6	21	(75.0)	16	(55.2)	0.117
	< 6	7	(25.0)	13	(44.8)	
	Missing	0		1		
Postpartum infection	Yes	0	(0.0)	7	(14.9)	0.015
Damage to bowel, urinary tract and bladder	Yes	6	(15.4)	8	(17)	0.838
ITU admission	Yes	31	(79.5)	19	(40.4)	<0.001
Infant outcomes		UK n(%) n=39		France n(%) n=47		
Perinatal mortality	*Yes*	1	(2.8)	1	(2.13)	0.999
	Missing	3		0		

***** Includes: arterial ligation and uterine compression sutures. Descriptive statistics calculated excluding the missing.

Table S5. Management and maternal and infant outcomes of women who had antenatally detected placenta praevia.

Management		UK n(%) n=86		France n(%) n=138		P-Value
PAS suspected prior to birth	Yes	64	(74.4)	86	(65.2)	0.149
	No	22	(25.6)	46	(34.8)	
	Missing	0		6		
Caesarean section	Yes	83	(96.5)	132	(95.7)	0.750
Caesarean hysterectomy	Yes	46	(53.5)	46	(33.3)	0.003
	No	40	(46.5)	92	(66.7)	
	Missing	0		0		
Total hysterectomy	Yes	56	(65.1)	66	(48.2)	0.013
	No	30	(34.9)	71	(51.8)	
	Missing	0		1		
Time between birth and hysterectomy	≤48hrs	53	(94.6)	53	(80.3)	0.019
	>48hrs	3	(5.4)	13	(19.7)	
No attempt to remove placenta after birth	Attempt	58	(67.4)	62	(45.3)	0.001
	No attempt	28	(32.6)	75	(54.7)	
	Missing	0		1		
Conservative approach: placenta left in situ	Yes	20	(23.3)	59	(42.8)	0.003
	No	66	(76.7)	79	(57.2)	
	Unknown			2		
How much left in situ	Complete	15	(75.0)	36	(61)	0.259
	Partial	5	(25.0)	23	(39)	
Had hysterectomy after left in situ	Yes	5	(25.0)	18	(30.5)	0.639
Pelvic arterial embolisation	Used	30	(34.9)	39	(28.3)	0.296
Other conservative surgery*	Used	18	(20.9)	23	(16.7)	0.422
Whole blood or Red blood cells received n(%)		64	(74.4)	77	(55.8)	0.005
In women who received whole blood or Red blood cells	median (IQR) unit	7	(4-12)	6	(3-11)	0.373
FFP received n(%)		47	(54.7)	60	(43.5)	0.103
In women who received FFP	median (IQR) units	4	(4-8)	5	(2-8)	
Platelets received n(%)		29	(33.7)	20	(14.5)	0.001
In women who received platelets	median (IQR) units	2	(1-2)	1	(1-2)	
Fibrinogen received	Used	21	(24.4)	48	(34.8)	0.102
Maternal outcomes						
Maternal mortality	Yes	0	(0.0)	1	(0.7)	0.999
Amount of blood loss *(mL)*	Median (IQR)	3000	(1500-7000)	1200	(500-2500)	
Postpartum haemorrhage (mL)	<3000	38	(44.2)	100	(76.3)	<0.001
	≥3000	48	(55.8)	31	(23.7)	
	Missing	0		7		
Severe postpartum haemorrhage (mL)	<2000	25	(29.1)	85	(64.9)	<0.001
	≥2000	61	(70.9)	46	(35.1)	
	Missing	0		7		
Massive transfusion (units)	≥6	43	(67.2)	38	(50.7)	0.049
	< 6	21	(32.8)	37	(49.3)	
	Missing	0		2		
Postpartum infection	Yes	2	(2.3)	3	(2.2)	0.953
Damage to bowel, urinary tract and bladder	Yes	10	(11.6)	15	(11)	0.891
ITU admission	Yes	67	(77.9)	50	(36.5)	<0.001
Infant outcomes		UK n(%) n=86		France n(%) n=138		
Perinatal mortality	*Yes*	2	(2.3)	3	(2.2)	0.999
	Missing	1		3		

***** Includes: arterial ligation and uterine compression sutures. Descriptive statistics calculated excluding the missing.

Table S6. Pregnancy characteristics and haematological management of women with PAS

Pregnancy characteristics		**UK n(%) n=134**		**France n(%) n=219**		P-value
Termination of pregnancy	Yes	2	(1.5)	1	(0.5)	0.559
	Missing	2		0		
Gestational age at birth	<34 weeks	23	(17.2)	39	(17.8)	0.874
	≥34 & <37 weeks	43	(32.1)	75	(34.2)	
	≥37 weeks	68	(50.7)	105	(47.9)	
Planned caesarean section	Yes	110	(83.3)	138	(63.0)	<0.001
	Missing	2		0		
Haematological management						
FFP received n (%)		69	(51.5)	88	(40.2)	0.038
In women who received FFP	median (IQR) units	4	(4-7)	4	(2-8)	0.716
Platelets received n (%)		43	(32.1)	29	(13.2)	<0.001
In women who received platelets	median (IQR) units	2	(1-2)	1	(1-4)	0.859
Fibrinogen received e.g. cryoprecipitate or fibrinogen conc.	Yes	34	(25.4)	69	(31.5)	0.219
Recombinant Factor VIIa used	Yes	5	(3.7)	3	(1.4)	0.148

Descriptive statistics calculated excluding the missing.