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ORIGINAL RESEARCH ARTICLE

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The relation between maternal obesity and placenta accreta spectrum: A multinational database study

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Abstract

Introduction: It has been suggested that women with obesity have increased risk of developing placenta accreta spectrum (PAS). It is unclear if this is independent of the increased risk of cesarean delivery seen with obesity itself. The aim of this study was to explore the association between maternal obesity and PAS, particularly severe PAS (percreta).

Material and methods: This is a cohort study based on cases recorded in the International Society for Placenta Accreta Spectrum (IS-PAS) database between April 2008 and May 2019. Multivariable logistic regression was used to explore the effect of maternal obesity on severity of PAS; this model was adjusted for other known risk factors including previous cesarean deliveries, maternal age, and placenta previa. The estimated rate of obesity in a hypothetical cohort with similar characteristics (previous

Abbreviations: BMI, body mass index; CD, cesarean delivery; IS-PAS, International Society for Placenta Accreta Spectrum; PAS, placenta accreta spectrum.

cesarean delivery and same parity) was calculated and compared with the observed rate of obesity in the women of the PAS cohort (one sample test of proportions).

Results: Of the 386 included women with PAS, 227 (58.8%) had severe disease (percreta). In univariable analysis, maternal obesity initially appeared to be associated with increased odds of developing the most severe type of PAS, percreta (odds ratio [OR] 1.87; 95% CI 1.14-3.09); however, this association was lost after adjustment for other risk factors including previous cesarean delivery (OR 1.44; 95% CI 0.85-2.44). There was no difference in the observed rate of obesity and the rate estimated based on the risk of cesarean delivery from obesity alone (31.3% vs 36.8%, respectively; $P = .07$).

Conclusions: Obesity does not seem to be an independent risk factor for PAS or severity for PAS. These findings are relevant for clinicians to provide accurate counseling to women with obesity regarding increased risks related to pregnancy.

KEYWORDS

abnormally invasive placenta, body mass index, obesity, placenta accreta spectrum, pregnancy

1 | INTRODUCTION

The incidence of women with placenta accreta spectrum (PAS: also known as abnormally adherent and invasive placenta) has dramatically increased globally over the last few decades.[1] The single most important risk factor for PAS is previous cesarean delivery (CD) with the risk rising with the number of previous CDs.[1] In combination with placenta previa, the risk of developing PAS after a single CD is 4%, this rises to 61% after four CDs. Other risk factors suggested include advanced maternal age, assisted reproductive techniques, and, recently, maternal obesity,[2] but as PAS still remains a relatively rare condition ascertaining a true connection can be challenging. This is important because identification of genuine risk factors may lead to a better understanding of the underlying pathophysiology leading to the development of PAS.

In parallel with the increase in CD, the prevalence of obesity is rising. A recent meta-analysis of five studies (including 554 106 pregnancies from Israel,[3] Japan,[4] Nordic countries,[5] the UK,[6] and the USA[7]), however, suggested that maternal obesity was a risk factor for occurrence of PAS (odds ratio [OR] 1.4; 95% CI 1.0-1.8).[2] Although this is biologically plausible, as obesity is linked to poor wound healing which could be a factor in the subsequent development of PAS,[8] it is difficult to separate this from the potential confounding influence of the significantly increased risk of CD for obese women.

Understanding the relationship between risk factors and PAS severity can help to uncover the underlying pathophysiology. Abnormally adherent placenta (accreta) is often seen after endometritis or repeated endometrial curettage but to develop abnormally invasive placenta (increta/percreta) a full-thickness scar is usually required.[9] There are currently no data available on the association between obesity and clinical severity of PAS.[10]

The aim of this study was to use cases from the International Society for Placenta Accreta Spectrum (IS-PAS) database to (a) explore the association between maternal obesity and clinical severity of PAS and (b) compare the observed rate of obesity within the PAS cohort with the expected rate of obesity for a modeled cohort with similar characteristics (previous CD and same parity).

Key message

Obesity in pregnancy does not appear to be associated with an increased risk of placenta accreta spectrum after accounting for effect of previous cesarean delivery.

2 | MATERIAL AND METHODS

This is a cohort study based on cases recorded in the IS-PAS FetView database; fourteen European and one non-European center (USA) provided cases retrospectively between 2008 and 2014 and prospectively collected data from 2014 to 2019. Cases were excluded from this study if PAS was suspected but not confirmed at delivery (PAS grade 1)[11] or the body mass index (BMI) was not recorded.

2.1 | Obesity and clinical severity of PAS

The primary outcome investigated was a comparison of the rate of obesity by clinical severity of PAS.[11] PAS grade 2 or 3 represents abnormal placentas, which remain fully within the uterus (accreta/increta); PAS grades 4, 5, or 6 were placentas that had reached the serosal surface or gone beyond it, potentially invading other pelvic organs (percreta; Figure 1). Obesity was defined according to WHO

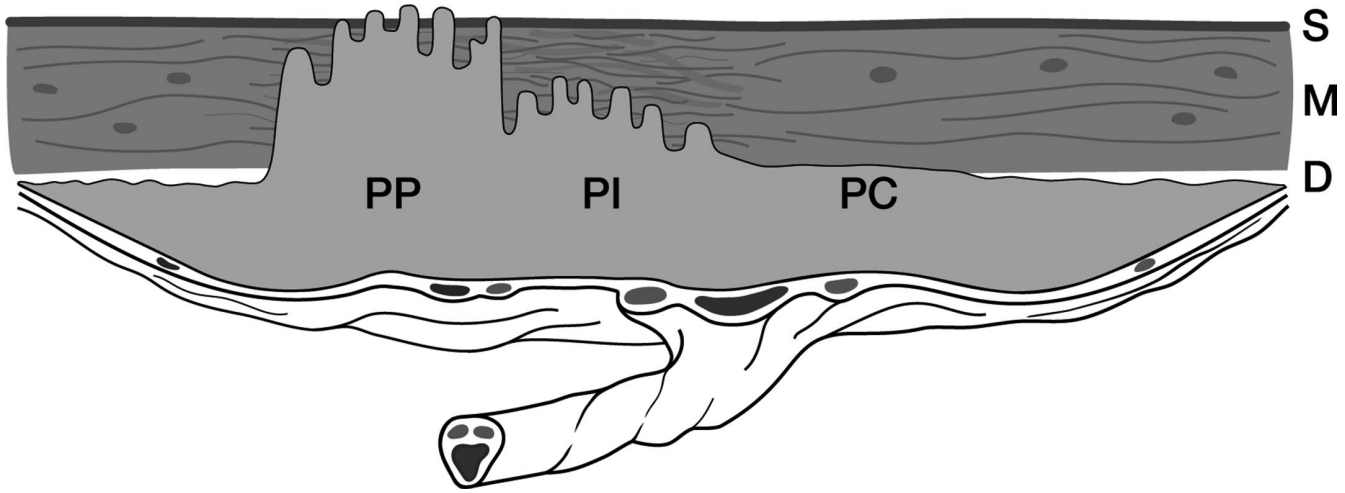

FIGURE 1 Diagram showing different levels of invasion of placenta accreta spectrum. Anterior placenta previa combining areas of normal and abnormal adherence and invasion to the uterine wall: creta (or accreta), increta, and percreta. D, decidua; M, myometrium; PC, placenta creta (or accreta); PI, placenta increta; PP, placenta percreta; S, serosa. Reproduced from: Jauniaux et al Placenta accreta spectrum: pathophysiology and evidence-based anatomy for prenatal ultrasound imaging. Am J Obstet Gynecol 2018;218(1):75-87 with permission from publisher

classification (BMI ≥30 kg/m^2). Maternal height and weight were measured at pregnancy "booking" in the first trimester. The main covariate considered was previous CD, given its predominant effect as a major risk factor for PAS. Other covariates included maternal age and placenta previa.

2.2 | Statistical analyses

The analysis was performed using all available data, following application of the exclusion criteria above. The distribution of continuous variables was explored using histograms, skewness, and kurtosis to identify any clear departure from a normal distribution. Data were described using mean (standard deviation) where it was normally distributed and median (interquartile range) where it was not. Logistic regression was used to assess the association of obesity with clinical severity of PAS in two groups; PAS contained within the uterus (accreta/increta, grades 2 and 3) with PAS breaching or extending beyond the uterine serosa (percreta, grades 4, 5, and 6). Multivariable regression analysis was used to adjust for the effect of previous CDs, maternal age, and placenta previa. Previous CD could be a confounder and a mediator in the association between obesity and PAS; in this analysis it was treated as a confounder to assess the independent/direct effect of obesity. Significance was assumed at a level of $\alpha < 0.05$.

2.3 | Underlying model to generate the expected obesity rate

Previous CD is the single greatest risk factor for PAS and demonstrates a clear dose response with the risk of PAS rising with the increasing number of CDs. Obesity is a major risk factor for CD. As BMI on average increases between pregnancies[12-14] the proportion of obese women has been demonstrated to rise with parity. Therefore, the intention of the model was to estimate the expected rate of obesity for a cohort of women with similar characteristics (previous CD and equivalent parity) and compare this with the observed rate of obesity in the women with PAS. Each estimated cohort is country specific. To reduce variance in the analysis due to small sample size, only countries that had submitted at least 25 cases to the database were included in the modeling. As the modeled cohort is based on the risk of obesity for women with previous CD, only women who had had a previous CD from the actual PAS cohort were included in this analysis.

Building a model to estimate the anticipated rate of obesity for a similar cohort to the actual PAS cohort required the following steps:

1. Identification of the country-specific underlying rates of maternal obesity and CD.
2. The conditional probability of obesity given one previous CD was calculated for each country based on that country's specific background obesity and CD rates, given that the risk of delivering by cesarean is doubled by obesity.[15]
3. The proportion of obese women expected for each parity cohort was calculated based on the country-specific conditional probability of obesity given one previous CD and the effect size seen for interpregnancy weight gain for each subsequent interpregnancy interval (up to four interpregnancy intervals).
4. A comparative group for each country was generated by matching the actual PAS cohort for parity to generate an estimated overall rate of obesity specific to a hypothetical cohort matched for parity.
5. The weighted average of the expected rate of obesity was calculated, weighted to the proportion of each country in the PAS

cohort; it was then compared with the observed rate of obesity in the cohort of women with PAS (using one sample test of proportion).

2.4 | Data used to estimate the expected obesity rate

1. The European Perinatal Health Report 2015[16] was examined to obtain the reported rates of maternal obesity and CD for each country. Information regarding rates of maternal obesity in Poland and Italy was not available in the European Perinatal Health Report 2015.[16] Therefore, they were obtained from a different report commissioned by the European Board and College of Obstetrics and Gynaecology;[17] for Italy, reported rates reflect data from the WHO database (2009) including a general female population aged 20 years or older.
2. The strength of the association of obesity (BMI ≥30 kg/m^2) and the risk of CD was obtained from an umbrella systematic review and meta-analysis by Kalliala et al; a relative risk of 2.00 (95% CI 1.87-2.15) was reported.[15]
3. Despite a considerable number of studies reporting interpregnancy increase in BMI, there is less information regarding the change in the rate of obesity according to number of previous pregnancies. Previous studies reported different interpregnancy increases in the rate of obesity with the effect size ranging between 3.5% and 6.5%.[12-14] For the primary analysis we assumed a variable effect as this was the rate quoted in the report most similar to our settings (increase in obesity rates of 4.9% between first and second pregnancies; 3.8% between second and third; 5.6% between third and fourth; 3.3% between fourth and fifth).[12] To explore the potential impact of the different rates on the association of obesity and PAS we performed a sensitivity analysis to explore the results seen when using an effect size varying between the lowest and highest rates quoted in the literature.

2.5 | Assumptions used to estimate the expected obesity rate

The assumptions that underlie the estimation are the following: (a) rate of obesity in nulliparous women is similar to the unselected population (information specificity for nulliparous women was not available in the European Perinatal Health Report 2015);[16] (b) the occurrence of a subsequent pregnancy is similar across BMI range; (c) the effect of a previous CD is consistent across countries and was accounted for only once per woman, assuming no cumulative effect; (d) the effect of interpregnancy interval in the rate of obesity is consistent across countries and is cumulative (up to four pregnancy intervals/previous pregnancies were accounted for).

All analyses were performed in STATA software, version 15.0 (StataCorp LP, College Station, TX, USA). This study has been reported in line with STROBE recommendations.[18]

2.6 | Ethical approval

Each center obtained individual local ethical approval to submit anonymized cases to the database. Details of these can be found in the online Supporting Information contained in the second Commentary of this supplement.[19]

3 | RESULTS

Of the 442 women included in the IS-PAS database, 32 (7.2%) were not confirmed to have PAS at delivery (grade 1) and 24 (5.4%) did not have their BMI recorded. Therefore, our study population included 386 women, of whom 227 (58.8%) had PAS grade 4, 5, or 6 placentas (percreta) and the remaining 159 had grade 2 or 3 placentas, which were fully contained within the uterus (accreta/increta: see Figure 2). For the modeling, 66 women (17.0%) did not have a previous CD and 80 (20.7%) were from countries who recorded fewer than 25 cases. Therefore, the final subgroup used for the modeling consisted of 240 women (see Figure 2).

3.1 | Obesity and clinical severity of PAS

The demographic characteristics and pregnancy outcomes of the study population are described in Table 1. Overall prevalence of obesity was 24.0% (93/386). The proportion of placenta percreta was 69.9% (65/93) in obese women and 55.3% (162/293) in non-obese women. Initial analysis appeared to indicate that obese women were more likely to have more severe PAS (grade 4, 5, or 6; percreta)

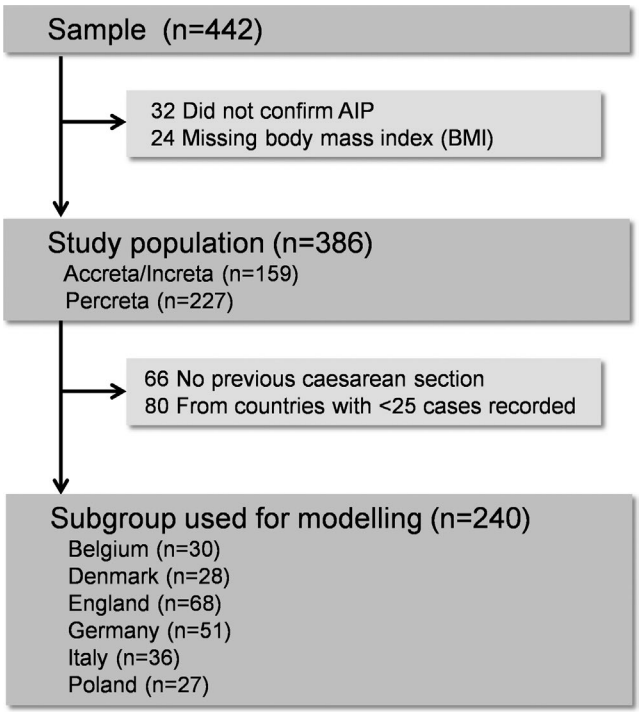

FIGURE 2 Study population. AIP, abnormally invasive placenta

(OR 1.87; 95% CI 1.14-3.09) (Table 2). However, when adjusted for other major risk factors, including number of previous CD, maternal age and placenta previa, this association was lost (OR 1.52; 95% CI 0.89-2.63).

3.2 | Observed and expected rates of obesity in the PAS population

Detailed demographic characteristics of the subgroup included in this component of the analysis are described in Supporting Information Table S1. A summary of the model assumptions and of the estimated and observed rates of obesity for each country, along with the weighted average, is provided in Table 3. In the primary model, there was no difference between observed and estimated rates of obesity (31.3% vs 36.8%, respectively; $P = .07$). In the sensitivity analysis that explored varying the effect size related to interpregnancy change in obesity rate, it was observed that PAS may be less likely to occur in women with obesity (ie, observed rate of obesity lower than expected rate of obesity) if the true interpregnancy change in rate of obesity is greater than 5.3% (Figure 3).

4 | DISCUSSION

To our knowledge, this is the first study to explore the association of obesity with the clinical severity of PAS; no relevant effect was observed (ie, women with obesity have similar severity of PAS

TABLE 1 Demographic characteristics of study sample

	All samples (n = 386) Mean ± SD or n (%)	Women without obesity (n = 293) Mean ± SD or n (%)	Women with obesity (n = 93) Mean ± SD or n (%)
Age[a]	34.6 ± 4.7	34.6 ± 4.7	34.5 ± 4.7
Previous CD			
0	66 (17.1)	33 (11.3)	3 (3.2)
1	154 (39.9)	103 (35.2)	25 (26.9)
2	95 (24.6)	82 (28)	33 (35.5)
≥3	71 (18.4)	46 (15.7)	15 (16.1)
Ethnicity[a]			
White	320 (87.7)	244 (88.4)	76 (85.4)
Black	21 (5.8)	13 (4.7)	8 (9)
Asian	24 (6.6)	19 (6.9)	5 (5.6)
Smoking at booking[a]	55 (16.4)	25 (16.9)	30 (16)
Pregnancy outcomes			
Cesarean delivery	363 (94)	276 (94.2)	87 (93.5)
Hysterectomy	263 (68.1)	192 (65.5)	71 (76.3)
MOH (>2000 mL)[a]	192 (52.5)	148 (53.2)	44 (50)
ICU admission (mother)	161 (41.7)	122 (41.6)	39 (41.9)
Maternal death	0 (0)	0 (0)	0 (0)
Infants (only singletons)[a]			
Preterm birth	288 (75)	214 (73.5)	74 (79.6)
Birthweight[b]	2590 (2205-2930)	2585 (2200-2930)	2608 (2250-2933)
Sex (male)	186 (52.2)	136 (50.7)	50 (56.8)
Apgar below 7 at 5 min	40 (10.9)	24 (8.6)	16 (18.2)
NICU admission	137 (35.5)	94 (32.1)	43 (46.2)
Stillbirth	11 (2.9)	6 (2.1)	5 (5.4)

Abbreviations: BMI, body mass index; CD, cesarean delivery; ICU, intensive care unit; MOH, major obstetric hemorrhage; NICU, neonatal intensive care unit.

[a]Missing data for age (n = 2), ethnicity (n = 21), smoking (n = 50), MOH (n = 20), preterm birth (n = 2), birthweight (n = 20), sex (n = 30), Apgar score (n = 19) and stillbirth (n = 12).

[b]Median and interquartile range provided.

TABLE 2 Effect of obesity, cesarean delivery, maternal age, and placenta previa on severity of PAS (logistic regression; n = 386)

	Unadjusted	Adjusted
	OR (95% CI)	OR (95% CI)
Obesity (BMI ≥30 kg/m^2)	1.87 (1.14-3.09)	1.52 (0.89-2.63)
Number of previous CD		
1	2.83 (1.53-5.23)	2.19 (1.16-4.16)
2	4.53 (2.30-8.90)	3.36 (1.65-6.82)
≥3	11.31 (5.02-25.49)	8.15 (3.52-18.86)
Maternal age >35 years	0.68 (0.45-1.02)	0.74 (0.47-1.14)
Placenta previa	3.20 (1.76-5.83)	2.40 (1.24-4.64)

Abbreviation: BMI, body mass index; CD, cesarean delivery; OR, odds ratio; PAS, placenta accreta spectrum.

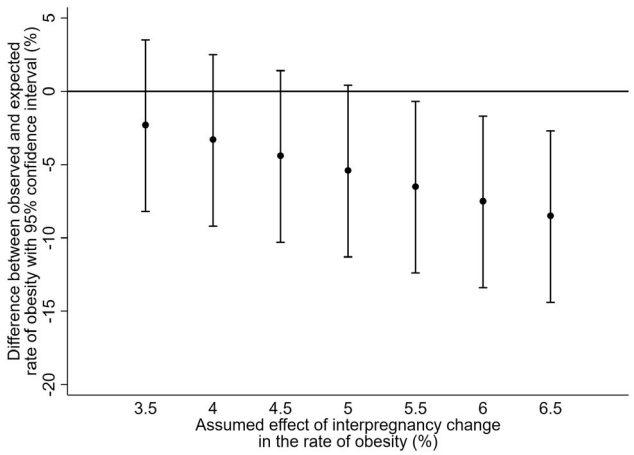

FIGURE 3 Sensitivity analysis exploring how variation in the interpregnancy increase in obesity rate influences the difference between the observed and estimated rates of obesity

compared with women with a BMI <30 kg/m^2). In addition, our modeled analysis suggests that obesity is not an independent risk factor for PAS but a co-factor acting by increasing the risk of CD. Published literature agrees that on average BMI increases between pregnancies and the reported size of this effect varies between 3.5% and 6.5%. However, the sensitivity analysis exploring the different effect sizes suggests that obesity is not associated with increased risk of PAS.

A recent meta-analysis has reported an association between obesity in pregnancy and PAS (OR 1.37; 95% CI 1.0-1.8),[2] although there is no consensus in literature.[3,6,8,20] It has been hypothesized that the underlying mechanism linking obesity to PAS is poor wound healing with increased risk of infection.[8] Most studies that have observed an increased risk of PAS associated with obesity have not appropriately adjusted for CD; therefore, this relationship could be confounded by the obesity-related increased risk of delivery by cesarean.[5] Indeed, our results suggest that no independent effect exists between obesity and PAS or its severity after accounting for previous CD. The sensitivity analysis has shown that obesity might even be protective against developing PAS if the interpregnancy increase in rate of obesity is actually greater than 5.3%; however, this needs to be interpreted with caution. Lack of a consistent definition of PAS cases in the literature also limits the generalizability of previous reports. This study has the advantage that the PAS diagnosis was made by an expert in a specialist center for PAS according to a strict set of predefined clinical criteria.

In modern obstetric practice, women have the right to be informed about their risks and choices providing opportunity for behavioral change and facilitating informed decision-making. Therefore, accurate identification of risk factors for conditions that can result in substantial morbidity, such as PAS, is of relevance. Presence of risk factors for PAS may help inform counseling of mode of birth and also provide opportunity for women to make informed decisions regarding their obstetric future. This is particularly

TABLE 3 Observed and expected rate of obesity in the PAS population

Country	Obesity (%) [a]	CD rate (%) [b]	Estimated proportion of obesity in a matched cohort (%) [c]	Observed proportion of obesity in women with PAS (%)	*P* value
Belgium	12.7	21.3	33.6	40.0	
Denmark	12.6	21.6	30.7	14.3	
England	21.2	27.0	45.7	30.9	
Germany	14.9	32.2	36.8	45.1	
Italy	15.0	35.4	36.6	22.2	
Poland	7.1	42.2	24.6	25.9	
Weighted average	15.3	29.7	36.8	31.3	.07

Abbreviations: CD, cesarean delivery; PAS, placenta accreta spectrum.

[a]From European Perinatal Health Report 2015 (https://www.europeristat.com/images/EPHR2015_web_hyperlinked_Euro-Peristat.pdf) or Devlieger et al, Eur J Obstet Gynecol Reprod Biol 2016;201:203-8. For Italy rate of obesity among women with reproductive age was used as no official rate of maternal obesity available;

[b]From European Perinatal Health Report 2015;

[c]Account for the increase in rate of obesity related to one previous cesarean delivery (estimated based on women with obesity having doubled risk for cesarean delivery (RR 2.00; 95% CI 1.87-2.15); Kalliala et al, BMJ 2017; 359: j4511) and interpregnancy interval (4.9% between first and second pregnancy; 3.8% between second and third; 5.6% between third and fourth; 3.3% between fourth and fifth; Ziauddeen et al, Sci Rep 2019;9:9175).

relevant for strong risk factors such as previous CD and placenta previa. Women with obesity are already at increased risk of many obstetric complications including preeclampsia, gestational diabetes, venous thromboembolism, and need to deliver by CD, as well as neonatal morbidity and mortality.[15] A recent evidence synthesis regarding perception of pregnancy risks in women with obesity has shown that women with obesity felt fearful of consultations because of the perceived stigma around being obese, which led to perceived over-inflation of the risks.[21] It is therefore important to clarify to clinicians that obesity is not associated with increased risk of PAS to avoid further unnecessary anxiety.

Cesarean delivery for women with obesity tends to have a longer operative time and is associated with increased risk of venous thromboembolism, wound infection/endometritis, and postpartum hemorrhage.[22-24] The urinary tract is a common site of injury during cesarean sections; however, ureteric stenting has not been shown to reduce the risk of such injuries in an observational study of women with PAS.[25] Despite no evidence of increase in risk of major organ injuries at hysterectomy for gynecological conditions in women with obesity,[26,27] cesarean hysterectomy can be a challenging procedure, particularly in these women. In our study, we have not observed an increase in maternal obstetric hemorrhage or admission to intensive care units related to obesity in women with PAS.

The strength of this study is the multinational IS-PAS database, which includes detailed characterization of women with PAS and a clear, predefined classification system for both diagnosis and grading of clinical severity. Limitations of this study are mainly related to uncertainties surrounding the modeled component of the analysis. There is limited literature on the interpregnancy change in the rate of obesity; most previous studies report the interpregnancy change in weight or BMI on a continuous scale only. We mitigated this uncertainty by performing sensitivity analyses with varying effect sizes. The other two potential effects on the rate of obesity that were not possible to model are the potential cumulative effect of previous CD (which would increase the expected rate of obesity) and the potential reduced rate of fertility in women with previous CD and obesity (which might reduce the expected rate of obesity).

5 | CONCLUSION

The apparent association between obesity and PAS appears to be confounded by the risk of CD conferred from having a high BMI. Obesity alone does not seem to be an independent risk factor for PAS or affect the severity of PAS. These findings are relevant for clinicians to enable them to counsel women with obesity regarding their increased risks related to pregnancy.

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CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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