

ORIGINAL RESEARCH ARTICLE

Prevalence of fetal anomalies, stillbirth, neonatal morbidity, or mortality in pregnancies complicated by placenta accreta spectrum disorders

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Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; IS-PAS, International Society for Placenta Accreta Spectrum; IVF, in vitro fertilization; NICU, Neonatal Intensive Care Unit; PAS, placenta accreta spectrum.

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Abstract

Introduction: Placenta accreta spectrum disorders (PAS) lead to major complications in pregnancy. While the maternal morbidity associated with PAS is well known, there is less information regarding neonatal morbidity in this setting.

The aim of this study is to describe the neonatal outcomes (fetal malformations, neonatal morbidity, twin births, stillbirth, and neonatal death), using an international multicenter database of PAS cases.

Material and Methods: This was a prospective, multicenter cohort study based on prospectively collected cases, using the international multicenter database of the International Society for PAS, carried out between January 2020 and June 2022 by 23 centers with experience in PAS care. All PAS cases were included, regardless of whether singleton or multiple pregnancies and were managed in each center according to their own protocols. Data were collected via chart review. Local Ethical Committee approval and Data Use Agreements were obtained according to local policies.

Results: There were 315 pregnancies eligible for inclusion, with 12 twin pregnancies, comprising 329 fetuses/newborns; 2 cases were excluded due to inconsistency of data regarding fetal abnormalities. For the calculation of neonatal morbidity and mortality, all elective pregnancy terminations were excluded, hence 311 pregnancies with 323 newborns were analyzed. In our cohort, 3 neonates (0.93%) were stillborn; of the 320 newborns delivered, there were 10 cases (3.13%) of neonatal death. The prevalence of major congenital malformations was 4.64% (15/323 newborns), most commonly, cardiovascular, central nervous system, and gastrointestinal tract malformations. The overall prevalence of major neonatal morbidity in pregnancies complicated by PAS was 47/311 (15.1%). There were no stillbirths, neonatal deaths, or fetal malformations in reported twin gestations.

Conclusions: Although some outcomes may be too rare to detect within our cohort and data should be interpreted with caution, our observational data supports reassuring neonatal outcomes for women with PAS.

KEYWORDS

fetal abnormalities, neonatal death, PAS, placenta, placenta previa, stillbirth

1 | INTRODUCTION

Placenta accreta spectrum (PAS) refers to a range of abnormal placentation in which the extravillous trophoblast firmly attach within a myometrial scar to a variable extent, and whereby the normal uterine architecture, elasticity and strength is disrupted, leading to placental bulging, fibrosis and hypervascularity along uterine surface.¹ The nomenclature categorizing PAS disorder severity clinically and by histopathology has been endorsed by the International Federation of Gynecology and Obstetrics (FIGO), including in its classification of the abnormally adherent placenta.^{2,3} This complex clinical entity is associated with significant maternal morbidity, not only due to hemorrhage but also due to the extension of placental tissue and fibrosis to the surrounding pelvic organs.⁴

Key message

Placenta accreta spectrum disorders are associated with neonatal morbidity risks associated with prematurity and fetal sequelae of maternal bleeding rather than a direct consequence of the placentation abnormalities, and the absolute risk of fetal malformations remains low.

Late preterm delivery is recommended between 34 0/7 and 36 6/7 weeks of gestation for PAS and must be individualized to the patient.⁵⁻⁸ The International Society for IS-PAS evidence-based guideline suggests expectant management until after 36 weeks'

gestation only for asymptomatic women with no obvious risk factors for preterm delivery, whereas planned delivery at 34 weeks' gestation is advised for women with a history of previous preterm birth, recurrent vaginal bleeding or preterm rupture of membranes.⁶ Earlier delivery may be necessary in the setting of or maternal or fetal compromise, such as with active bleeding or suspected uterine rupture. There is little evidence regarding neonatal outcomes in PAS cases. Most studies focus on maternal outcomes, surgical techniques, and antenatal diagnosis. In our first analysis of the IS-PAS database which included cases collected from 2008 to 2019, neonatal outcomes were compared between planned versus emergency cesarean deliveries, with no significant differences found other than lower neonatal birthweights and longer time spent in the Neonatal Intensive Care Unit (NICU), in the emergently delivered cohort, which had more neonates delivered before 34 weeks' gestation.⁹

The aim of this study was to describe the neonatal outcomes (fetal malformations, neonatal morbidity, twin births, stillbirth, and neonatal death) in an international multicenter database of PAS cases.

2 | MATERIAL AND METHODS

This is a multicenter cohort study based on prospectively collected cases from the multicenter database of IS-PAS, carried out between January 1, 2020 and June 30, 2022 by 23 centers from 16 countries in Europe, Asia, North, and South America (REF EDITORIAL on the same ACTA supplement).

Data were collected via chart review using a standardized, secured and password-protected online data collection platform (FetView, Zeitgeist Health SE, Prague, Czech Republic) which contains structured case data and reports, but no images. PAS grading was concordant with FIGO clinical staging and cases were classified by the most severe grade present, if more than one grade within the same case was identified. Cases were screened and managed according to each center's own protocol without any interference from the society. Local Ethical Committee approval and Data Use Agreements were obtained according to local policies.

All individuals with prenatal or intrapartum diagnosis of PAS were eligible for inclusion. Singleton and multiple gestations were included, but terminations were excluded. Cases in which PAS was not confirmed clinically or by histopathology, or when data regarding the neonatal outcomes were missing, were excluded. Data collected regarding neonatal outcomes included birthweight, stillbirth, APGAR score at 5 min, complications of prematurity (respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, severe jaundice), infection, hypoxic ischemic encephalopathy, and admission to the Neonatal Intensive Care Unit. Birthweight was converted to percentiles according to the neonatal curves applied in each center.

For the purpose of this study, we defined a major fetal or neonatal malformation as a life-threatening structural anomaly likely to cause significant impairment of health or functional capacity without

medical or surgical treatment, whereas minor malformation was identified, but unlikely to cause significant impairment.¹⁰ Stillbirth was defined as the delivery of a neonate with no signs of life, known to have died before delivery and after 20 completed weeks of pregnancy.¹¹ Neonatal death was defined as death occurring in the first 4 weeks after the birth.¹² Major neonatal morbidity was defined as a composite including APGAR score at 5 min <7, complications of prematurity (respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, severe jaundice), infection, hypoxic ischemic encephalopathy, and admission to the NICU. No statistical analysis was performed as this is a descriptive study.

3 | RESULTS

During the study period, 315 pregnancies were eligible for inclusion; there were 12 twin pregnancies in the database, totaling data from 329 fetuses/newborns; 2 cases were excluded due to data inconsistencies regarding fetal abnormalities. In our database, there were 4 cases of termination of pregnancy, one due to Trisomy 21 (17 weeks of gestation), one due to preterm premature rupture of membranes (22 weeks), one cesarean scar pregnancy (12 weeks), and in one case, the reason for termination was not stated (21 weeks). After excluding pregnancy terminations there were 311 pregnancies with 323 newborns analyzed. The median gestational age of delivery in our population was 35 weeks, ranging from 22 to 41 weeks; in women who had peripartum hysterectomy median gestational age of delivery was 35 weeks (34–36, $n=186$), 36 weeks (35–38, $n=38$) in women with focal resection of the myometrium and 37 weeks (36–37, $n=10$) for women with placenta in situ. Median neonatal birthweight was 2474 g (129–4280), with 15 cases with a birthweight less than the 3rd percentile (5.1% of our population, from the 291 with complete information) and 57 cases with a birthweight above the 90th percentile. Maternal and neonatal characteristics are summarized in Table 1.

In our cohort, 3 of 323 neonates (0.93%) were stillborn; two were in the setting of severe maternal hemorrhage (22 and 31 weeks of gestation), and in one case, no clear preceding cause for stillbirth was identified (32 weeks). Within the 320 newborns delivered alive, there were 10 cases (3.13%) of neonatal death, 5 due to complications of extreme prematurity (delivery between 22 and 24 weeks), 3 from fetal malformations (anencephaly, hypoplastic left heart syndrome, and gastroschisis) and 2 because of neonatal sepsis (delivered at 30 and 35 weeks of gestation).

The prevalence of major congenital malformations in our population was 4.64% (15/323 newborns), and included cardiovascular (the most common), central nervous system, and gastrointestinal tract malformations (Table 2). The majority of malformations (10/15) were in women with PAS FIGO grades 2 and 3.

The overall prevalence of major neonatal morbidity in pregnancies complicated by PAS was 47/311 (15.1%). In the case of births in the periviable period (defined in this study as births between 22 and 24 weeks of gestation) the main complications found were

TABLE 1 Maternal and neonatal characteristics.

Age [years]	35 (19–48)
Weight [kg]	73 (31–177)
Height [cm]	164 (134–185)
BMI kg/m ²	27.2 (11.4–45.8)
Gestational age at delivery [weeks]	35 (12–41)
Ethnicity [%]	
White	63.5
Black	10.5
Mixed	5.7
Asian	4.1
Mediterranean	1.6
Arabic	2.9
Not stated or unknown	11.7
Previous pregnancies [n]	3 (0–14)
Previous deliveries [n]	1.9 (0–11)
Previous c-sections [n]	1.6 (0–6)
Previous D&C [n]	0.6 (0–5)
Twin pregnancies gestational age at delivery [n]	
29–33 + 6 weeks	7
34–36 + 6 weeks	3
>37 weeks	2

respiratory distress syndrome and intraventricular bleeding; regarding early preterm births (between 24 and 34 weeks), there were 31 complications out of 84 births; lastly there were 32 complications in the late preterm birth group (34–36 weeks of gestation) and 10 in the group born after 36 weeks of gestation. There were 38 cases of APGAR score at 5 min < than 7, 11 cases (13.5% from the total of FIGO 1 cases) in PAS FIGO 1, 8 (10.7%) in FIGO 2 and 19 (12.5%) in FIGO 3 (10 3a, 6 3b and 3 3c). The complications with an indication of week of gestation at delivery are presented in Table 3.

In our cohort, there were 12 twin pregnancies (3.81%). There were no stillbirths, neonatal deaths, or fetal malformations in this group. Considering major neonatal complications, respiratory distress syndrome affected 7 of the twin newborns (29.2%) and severe jaundice 3 cases (12.5%); the gestational age at the delivery ranged from 22 to 37 weeks, with a mean of 32 weeks (Table 1).

4 | DISCUSSION

In this large cohort of women with PAS from multiple centers in different countries, the majority of fetal complications are due to complications of prematurity, a majority of which was in the late preterm period and due to indicated preterm delivery. Even though we do not have an adequate comparison group within our database, we believe our data is reassuring for women with PAS when treated in centers with experience with the disorder.

The stillbirth rate from our experienced PAS centers was 0.93%. This is only slightly higher than the stillbirth ratio for the general

TABLE 2 Description of fetal malformations diagnosed in women with PAS.

Fetal malformation	N = 15	FIGO Grade
Cardiovascular	7	
Tetralogy of Fallot	2	1; 3b
Hypoplastic left heart syndrome	1	3b
Ventricular septal defect	1	1
Atrioventricular septal defect	1	1
Pulmonary valve stenosis	1	1
Coarctation of the aorta	1	3a
Abdominal wall	1	
Gastroschisis	1	3a
Gastrointestinal tract	3	
Severe intestine dilation	1	2
Mesenteric cyst	1	1
Fistula tracheo-esophageal	1	3b
Central Nervous System	3	
Anencephaly	1	3a
Fronto Cerebellar hypoplasia	1	2
Arnold-Chiari syndrome	1	2
Multiple malformations	1	
Airway obstruction from neck mass, hypognathia	1	3b

Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.

population in the United States of America (from 1/160–1/200)¹³ and quite comparable to an estimated global pooled stillbirth rate (after 28 weeks of gestation) published in Lancet of 13.9/1000 total births, ranging from 22.8/1000 in central Africa to 2.9/1000 in western Europe.¹⁴ It is important to consider whether PAS confers an increased risk of neonatal morbidity and mortality, both for patient counseling and for care planning and management. There remains a paucity of information regarding the stillbirth rate in PAS, with inconsistencies in the results presented. In a study by Nieto Calvache et al.¹⁵ during the study period between April 2016 and December 2017 in Colombia, there were 3 cases of fetal death out of 62 women (4.8%) with their dedicated PAS team; in a retrospective study from a Canadian tertiary referral center with 12 years of data, the stillbirth rate was 6.4%,¹⁶ whereas Shamshirsaz et al. reported no cases of stillbirth in their study.¹⁷ Vinograd et al. from Israel. reported an adjusted OR for perinatal mortality (which includes neonatal deaths, not only stillbirths) of 2.9, 95% CI 1.7–4.87, when compared to the general population.¹⁸ Baldwin et al., in a population-based record linkage study from Australia, found an increased risk of stillbirth (RR 5.4, 99% CI 4.0–7.3) and neonatal death (RR 8.0, 99% CI 1.5–41.6) in women with PAS, compared to the general population.¹⁹ Differences in reported rates may be attributed in part to variability in study inclusion and exclusion criteria, delivering facility and team experience, and regional practices.

With regard to neonatal mortality, at least 7 out of the 10 cases in our database were linked to sequelae of prematurity or from sepsis. This supports the idea that the abnormality in placentation is

TABLE 3 Neonatal complications according to gestational age at delivery.

	22+0–23+6 weeks	24+0–34+0 weeks	34+1–36+0 weeks	>36+ weeks
	N = 6	N = 84	N = 122	N = 111
RDS	2/6 (33.3%)	17/84 (17.9%)	17/122 (13.82%)	4/111 (3.6%)
Intraventricular bleeding	2/6 (33.3%)	4/84 (4.8%)	1/122 (0.08%)	0
Necrotizing enterocolitis	0/6	2/84 (2.4%)	0	0
Severe jaundice	0/6	3/84 (3.6%)	11/122 (8.94%)	4/111 (3.6%)
Severe infection	0/6	5/84 (6.0%)	3/122 (2.44%)	2/111 (1.8%)

Abbreviation: RDS, respiratory distress syndrome.

not directly responsible for an increase in neonatal mortality, but rather is indirectly associated with indicated preterm delivery, especially in the setting of antenatal maternal hemorrhage.²⁰ While ours is a time-limited cohort, overall, the risk of intrauterine or neonatal death appears reassuringly low for PAS patients who are treated in referral centers.

Little is published about fetal and neonatal malformation rates, especially in the setting of PAS. Our data revealed only a slightly higher malformation rate than the expected of 2.58% reported by EUROCAT, a European network of population-based registries for the epidemiologic surveillance of congenital anomalies.²¹ This slightly higher prevalence of congenital anomalies in our study compared to the EUROCAT published rate may be due to the higher maternal age and parity of PAS patients as well as due to the presence of placenta previa. Placenta previa, according to some studies, may be associated with an increased risk of fetal malformations, even though this is still debated.²² Hypoxia is normal in the earlier stages of embryo development, at least until remodeling of the spiral arteries occurs.²³ Fibrosis in a uterine scar may cause low oxygen concentrations to persist beyond the first stages of embryo development. There is some evidence that hypoxia may be associated with defects in fetal organogenesis, particularly cardiac malformations.²⁴ Hypothetically, abnormal placentation in PAS may be associated with fetal malformations due to hypoxia in the implantation site (in the fibrotic areas of uterine scars) or small episodes of bleeding that may disrupt organogenesis; however, further studies are needed to explore this.²² Finally, it is possible that some women with PAS were first referred to our participating centers for a higher level of care for a fetal indication, after which PAS was detected on detailed antenatal imaging.

Besides preterm birth, the most common neonatal complications in our population were respiratory distress syndrome, severe jaundice, and severe infection. These complications are mainly related to prematurity, as PAS pregnancies are often delivered before term to reduce maternal morbidity and mortality.⁶ However, in the study by Baldwin et al.¹⁹ infants (both preterm and term) born to mothers with PAS were at increased risk of neonatal morbidity and resuscitation, with the study by Moeinia et al. also reaching similar conclusions, even after adjusting for confounders.²⁵ We have previously reported that emergent delivery was associated with lower median gestational ages.⁹ A recent systematic review and meta-analysis

confirmed our results, stating that emergent deliveries were associated with lower gestational ages at birth, lower birthweights, and higher NICU admissions.²⁶ Our reported range of birthweight below the 3rd percentile 3 is similar to that reported in the literature for the general population, showing that even though PAS is a placental disease, it doesn't seem to affect fetal growth.²⁷

The findings in this study suggest that adverse neonatal outcomes in the setting of PAS are not likely due to the abnormalities in placentation but rather with sequelae of prematurity.

Compared to the general population, our twin birth rate is only slightly higher than the twin birth rate reported in the United States of America, which was 32.6 twins per 1000 total births in 2018.²⁸ Interestingly, in the study by Miller et al. the prevalence of PAS was 41.6/10000 in twin pregnancies and only 11.8/10000 in singleton pregnancies. In their regression model, there was a positive association between multiple pregnancies and PAS (aRR 2.96, 95% CI 2.23–3.93) and a higher probability of PAS without placenta previa in these gestations.²⁹ In a recent systematic review and meta-analysis, 58.14% (95% CI 42.1–73.0) of twin pregnancies with PAS were conceived by in vitro fertilization (IVF) and were less likely to have prenatal diagnosis of PAS, whereby PAS was identified antenatally only in 27.9% (95% CI 15.3–43.7) of cases.³⁰ IVF is traditionally associated with a higher risk of multiple pregnancies and fetal anomalies. It is possible that endometrial microtrauma associated with IVF (associated with a higher probability of live birth³¹) may have an impact on the integrity of the decidua, leading to an increased risk of PAS in locations different than the traditional ones, explaining the lower association with placenta previa. Unfortunately, we do not have adequate information regarding medically assisted reproduction cases in our database. It is also possible that the increased placental surface may lead to implantation in areas without decidua, leading to the abnormal placentation with previous endometrial trauma. In these cases, there is a higher probability that PAS goes unnoticed until delivery, possibly explaining the association found between these cases and a higher need for red blood cells when compared to PAS cases in singleton pregnancies.³²

Importantly, clinicians should carefully evaluate placenta(s) in multiple gestations, not only for risks associated with chorionicity and amnionity but also for evaluation of the risk of abnormal placentation including PAS, even if the placenta is located away from a cesarean scar.

5 | CONCLUSION

Our study aimed to evaluate the association of PAS with fetal malformations, stillbirth and neonatal death, and neonatal morbidity, using a large international multicenter database of women with PAS. Because of the nature of our database and without a control group, this is not a comparison study of relative risk, but rather a survey of the data we collected within our centers. While PAS may increase the risk of some of these outcomes, the absolute rates of fetal and neonatal morbidity and mortality remain low and mainly related to prematurity. Further prospective and adequately powered studies are needed to evaluate any potential causal relationship between the abnormal placentation in PAS and hypoxia or other pathophysiologic mechanisms with fetal malformations, stillbirths, neonatal deaths, or other neonatal adverse outcomes.

AUTHOR CONTRIBUTIONS

Pedro Viana Pinto: Conceptualization, investigation, methodology, project administration, visualization, writing—original draft. Katarzyna Kawka-Paciorkowska: Conceptualization, investigation, methodology, project administration, visualization, writing—original draft. Maddalena Morlando, Hubert Huras: Magdalena, Kořak, Charline Bertholdt, Andrzej Jaworowski, Thorsten Braun, Karin A. Fox, Olivier Morel, Alexander Paping, Vedran Stefanovic, Mina Mhallem, and Heleen J. Van Beekhuizen: Resources, validation, writing—review & editing. All IS-PAS Group collaborators contributed by filling the forms with own cases, giving suggestions during preparation of manuscript, and approved the final version.

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CONFLICT OF INTEREST STATEMENT

None.

ETHICS STATEMENT

All participating centers were responsible for contributing to clinical and scientific research under local IRB/ethics committee approval and operated under Data Use Agreements between individual centers and the IS-PAS. Details of these have been published previously.³³

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