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PREGNANCY

ORIGINAL RESEARCH

Investigating and quantifying selection bias in research using placental pathology samples

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Abstract

Introduction: Increasing research interest has focused on placental pathology and pregnancy outcomes. Placental pathology examinations that are requested by the delivering provider are often used for research due to convenience, potentially introducing selection bias. We leveraged a large cohort of prospectively collected and examined placentas to compare prevalences of placental pathology and to quantify potential selection bias.

Methods: All placentas were prospectively collected from participants and pathology examinations were completed in the Stress, Pregnancy, and Health (SPAH) study, regardless of delivering provider request. In all cases, placental pathology was categorized and graded into four major groups: acute inflammation (AI), chronic inflammation (CI), fetal vascular malperfusion (FVM), and maternal vascular malperfusion (MVM). We compared the distribution of placental pathology in cases with and without pathology examination requests. Odds ratios (OR) for preterm birth (PTB) and small for gestational age (SGA) infants were calculated in the whole cohort and compared with the requested subset. Relative odds ratios (ROR) were used to quantify the magnitude of selection bias. Models were adjusted for sociodemographic and pregnancy characteristics.

Results: A total of 575 placentas were collected and examined, 287 with delivering provider examination request and 288 without request. The prevalence of AI, CI, and FVM was similar among the two groups. However, the prevalence of MVM was significantly higher in the requested placentas, particularly for high-grade MVM

(15% vs. 8%, $p < 0.01$). In adjusted models, MVM was significantly associated with increased odds of PTB in the whole SPAH cohort and the requested subset (SPAH OR: 3.07, 95%CI: 1.76,5.35; requested OR: 3.34, 95%CI: 1.74,6.38). MVM was also significantly associated with SGA infants (SPAH OR: 3.72, 95%CI: 1.55,8.95; requested OR: 4.18, 95%CI: 1.36,12.9). RORs were 1.09 for PTB and 1.12 for SGA, indicating 9% and 12% overestimation in a provider-requested sample. When considering grade of pathology, selection bias had the greatest impact on the association between PTB and high-grade MVM.

Conclusions: MVM was the only placental pathology seen more frequently in the delivering provider requested sample. Our RORs quantify differences in the associations, providing an estimate for the potential impact of selection bias. Research using a convenience sample of requested placentas may modestly overestimate associations, though the overall findings and interpretation of associations remain unchanged.

KEYWORDS

adverse pregnancy outcomes, indications for placental examination, maternal vascular malperfusion, placenta, selection bias

1 | INTRODUCTION

A functioning placenta is a critical requirement for a healthy pregnancy. Placental pathology offers an avenue for understanding pregnancy and its outcomes by describing the patterns of injury present in the placenta. Perinatal pathology guidelines recommend placental evaluations begin with a gross examination, followed by low-magnification injury assessment, and finally a higher magnification examination to grade and stage pathology patterns and identify specific lesions [1]. Specific guidelines are outlined in the Amsterdam placental workshop group consensus statement, which brought together perinatal pathology experts to standardize sampling of the placenta and clarify definitions of placental lesions [2]. The placental pathology report provides information that is clinically relevant for maternal and infant health, such as underlying causes related recurrent preterm birth and pregnancy loss. Therefore, placental findings are relevant to several types of clinicians, including delivering obstetrical providers, maternal-fetal medicine specialists, neonatologists, child neurologists, and geneticists [3].

Despite these many positives, placentas are one of the few specimens that do not have a requirement to be sent to pathology following a procedure. It is currently not feasible to examine all placentas following delivering, due to the prohibitive cost of such a labor-intensive effort, and the limited expertise in perinatal pathology. Placentas are typically reviewed by a pathologist only if there is significant maternal disease or an adverse pregnancy outcome. These examinations are requested by the delivering provider due to clinical indications during pregnancy, labor and delivery, and/or postpartum [4]. The placentas delivered in healthy patients after a normal pregnancy course with no adverse pregnancy outcomes are usually discarded unless the patient takes it home, leaving a gap in the information about placentas of uncomplicated pregnancies (Figure 1A). Therefore, pregnancies with adverse pregnancy and neonatal outcomes are overrepresented among samples derived from clinically requested placental examinations [5].

Research into associations between adverse pregnancy outcomes and placental pathology frequently uses placental pathology data gathered from these clinically indicated pathology examinations. Since selection into this sort of research sample is dependent on the adverse outcome, a selection bias may be introduced. To our knowledge, the magnitude of this selection bias has not been quantified, leaving an uncertainty about just how much the selection bias impacts our understanding of associations between placental pathology and adverse pregnancy outcomes. Understanding the potential impact of selection bias is important for interpreting associations that leverage retrospective placental pathology reports.

In this analysis, we leverage a cohort of prospectively collected placentas, all of which were examined with the same standardized gross and microscopic examination protocol, to compare the distribution of placental pathology between the subset of placentas that had an examination request by the delivering provider and

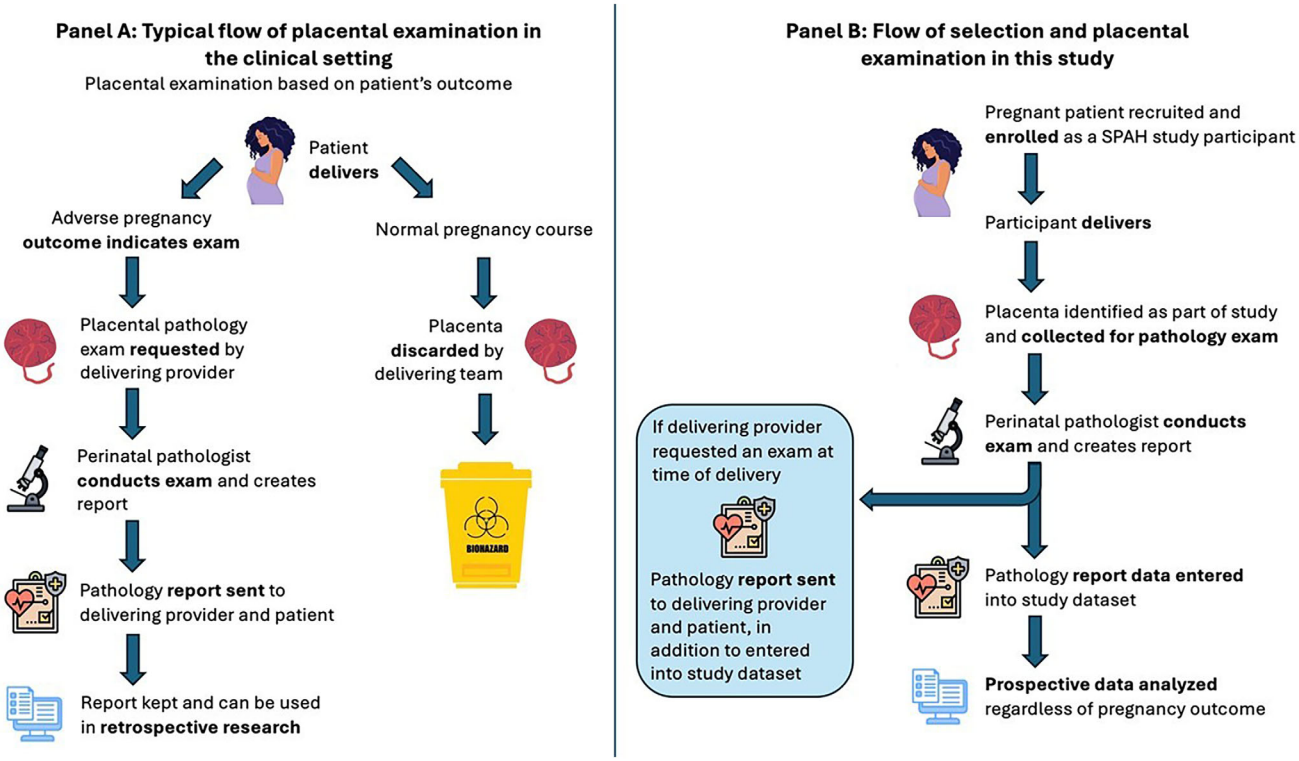

FIGURE 1 Workflows of placental examinations: comparison of typical clinical workflow and research study workflow.

placentas that were examined without a request. We additionally estimate associations between placental pathology and adverse pregnancy outcomes using the requested subset compared to the full, prospectively collected placenta sample, which was not selected based on the presence of an adverse pregnancy outcome.

2 | MATERIALS AND METHODS

2.1 | Study sample

We prospectively recruited patients into the observational Stress, Pregnancy, and Health (SPAH) study at a single institution between 2018 and 2023. Patients met eligibility criteria if they were 18 years of age or older, less than 25 weeks gestation according to ultrasound, had a singleton pregnancy, spoke English, and were planning to deliver at the institution's hospital. Patients were considered ineligible if they were on chronic corticosteroid treatment at the time of enrollment (not including inhalers or topical steroids). Patients were excluded if there were known fetal congenital anomalies or chromosomal abnormalities. Our sample was recruited to match the institution's pregnant population. Participation in the study included two research visits, the first between 20 and 26 weeks gestation and the second after 28 weeks gestation. Following delivery, placentas were collected and pregnancy outcomes were abstracted from electronic medical records (EMR). Patients provided written informed consent and the SPAH study was approved by [NorthShore University Heathsystem] and [Endeavor Health and Northwestern University] Institutional Review Boards.

2.2 | Placental examination

Placentas from all enrolled patients were prospectively collected and delivered to the Department of Pathology and Laboratory Medicine for examination. All placentas, regardless of whether pathology examination was requested by the delivering provider or not, were collected as participants delivered, handled following the same study procedures regarding gross and microscopic examination, and examined by a single perinatal pathologist (LME). LME was not blinded to whether the delivering provider requested a pathology examination. If a review was requested, a final pathology report was generated and released to the delivering provider and the patient that gave birth. If a placental pathology examination was not requested by the delivering provider, the pathology report was only used for research purposes and not shared with the provider or patient (Figure 1B).

For all placentas, regardless of provider request for placental pathology, gross examination was performed by qualified pathologists' assistants who followed a grossing standardized protocol in all cases. In brief, the gross examination included the placental weight, insertion, length, and coiling of the umbilical cord, membrane insertion type and description of any membrane discoloration, characterization of any fetal and maternal surface abnormalities, and size and location of any parenchymal lesions. Histologic sections included samples of the membranes, umbilical cord, 2 full thickness parenchymal sections, 3 maternal surface biopsies and representative samples of all parenchymal lesions. Hematoxylin- and eosin-stained slides were reviewed for all cases by a single perinatal pathologist (LME). Placental pathology was categorized and graded based on four major pathology groups: acute inflammation (AI), chronic inflammation (CI), maternal vascular malperfusion (MVM), and fetal vascular malperfusion (FVM). Categorization and grading were done by a single perinatal pathologist, utilizing standardized, well-defined, and up to date diagnostic criteria [2, 6], limiting subjectivity in interpretation.

Data was additionally abstracted from the "reason for placental exam" field in the labor and delivery summary in the EMR for placentas that were requested to be examined by pathology. Our institution's guidelines for delivering providers to request a pathology examination include the following indications: chorioamnionitis, intrauterine growth restriction, preeclampsia, multiple gestation, abnormal meconium, maternal or neonatal death, premature birth before 34 weeks gestation, insulin dependent diabetes, emergency cesarean section, fetal anomaly, abruption, placenta previa, cord gas pH below 7, 5-min Apgar score below 7, infant special care unit (ISCU) admission, compromised fetal status, and "physician or delivery provider request".

2.3 | Adverse pregnancy outcomes

Adverse pregnancy outcomes (APOs) of interest included preterm birth (PTB), defined as birth < 37 weeks gestation, and small for gestational age (SGA) infant, defined as a birthweight < 10^{th} percentile for gestational age and sex based on Fenton growth curves [7]. Gestational age, birthweight, and fetal sex were abstracted from infant's EMR following delivery.

2.4 | Covariates

At the first study visit, participants were interviewed about their sociodemographic characteristics, including age, race/ethnicity, and socioeconomic position. Height and weight were also measured to calculate second trimester body mass index (BMI). Clinical characteristics were abstracted from study participants' and their infants' EMR following delivery. Data included participant's medical history, mental health history, medication usage, and prenatal care; obstetric information, such as hypertensive disorders of pregnancy, infections during pregnancy, type of delivery, gestational age at delivery, and delivery complications; infant's weight, length, and head circumference, admission to the ISCU and length of stay, other infant complications, Apgar scores, and feeding methods.

2.5 | Analysis

For our primary analysis, placentas were categorized as either "requested" if a delivering provider requested an examination or "not requested" if the placental examination only occurred due to the delivering patient's participation in the SPAH study. We compared the clinical and demographic characteristics and prevalences of the four major pathology domains by grade of the pathology between these two groups. We then examined how each pathology category was associated with odds of PTB and SGA infants by comparing the pathology-requested sample with the full SPAH cohort.

Differences in demographic, clinical, and pathologic characteristics between groups were analyzed using chi-square tests. Associations between placental pathology and adverse pregnancy outcomes (PTB, SGA infant) were estimated using logistic regression. These models were repeated and adjusted for potential confounders of the relationship between placental pathology and adverse pregnancy outcomes (PTB and SGA infant) based on the literature, including BMI, race and ethnicity, maternal age, cesarean section, and parity [8–13].

Relative odds ratios (RORs) were used as a simple calculation to quantify selection bias [14]. The ROR is calculated dividing the individual requested ORs by the full SPAH cohort ORs, with an ROR of 1 indicating no selection bias. For associations > 1, an ROR < 1 indicates that the subsample underestimates the association, and an ROR > 1 indicates that the subsample overestimates the association (for associations < 1, the reverse is true).

Analyses were completed on IBM SPSS Statistics Version 29.0.2.0 and an alpha level of 0.05 was used to determine statistical significance.

Data will become available upon publication of the main study aims, per National Institutes of Health Guidelines. At the time of submission, data are currently available upon proposal request to the research group.

3 | RESULTS

3.1 | Study sample

The SPAH study enrolled 605 patients. Of these, we collected placentas at delivery and birth outcomes data for 575 (95%) patients. Placental collection was missed in 30 cases due to the delivery occurring at an outside institution, placenta accidentally discarded, or due to patient preference to keep their placenta. Of the 575 placentas that were examined grossly and histologically for the SPAH study, 288 (50.1%) placentas were categorized as placental pathology examination "not requested", and 287 (49.9%) placentas had an accompanying request by a delivering provider and were categorized as placental pathology examination "requested".

The majority of provider requests for placental pathology examination ($n = 189$, 65.8%) did not indicate the clinical indication for placental examination in the labor and delivery field of the EMR. Of the 287 placentas requested, 98 (34.1%) had at least one indication for placental pathology examination listed in the EMR field; some had two indications. The most common indication for request was gestational hypertension and preeclampsia ($n = 22$,); followed by COVID infection during pregnancy ($n = 17$); confirmed or suspected chorioamnionitis ($n = 17$); gestational diabetes ($n = 16$); diabetes ($n = 11$); chronic maternal health condition ($n = 8$); meconium ($n = 6$); chronic hypertension ($n = 5$); history of prior pregnancy complication ($n = 5$); intrauterine or fetal growth restriction ($n = 4$); preterm delivery ($n = 4$); concern for abruption ($n = 4$); advanced maternal age, hypothyroidism, marginal cord insertion, and oligohydramnios (each $n = 2$). Other reasons (only 1 indicated the following as a reason for request) included cholestasis, fetal cardiac anomaly, fetal intolerance of labor, postpartum hemorrhage, smoker, placenta previa, preterm premature rupture of membranes, possible Herpes simplex virus infection, cord prolapse, and retained placenta.

3.2 | Comparison of demographic and pathology characteristics

Patients for whom placental pathology examination was requested by the delivering provider had higher BMI, higher prevalence of cesarean section, hypertensive disorder of pregnancy, diabetes mellitus, preterm delivery, and clinical chorioamnionitis than those for whom placental pathology examination was not requested (Table 1). Furthermore, infants of mothers in the placental pathology examination requested group had significantly lower birthweight and a higher prevalence of SGA infant and ISCU admission.

The prevalences of AI, CI, and FVM and placental size were similar among those with and without placental pathology requests (Table 2). The prevalence of MVM was significantly higher in the placentas requested to be examined compared to those not requested. MVM was present in 35% of requested versus 24% of not requested, low-grade MVM was present in 20% of requested versus 15% of not requested, and high-grade MVM was present in 15% of requested versus 8% of not requested ($p = 0.002$).

3.3 | Assessing selection bias associated with APOs

Of the 575 participants, 66 (11.5%) delivered preterm; 60 of these had a delivering provider request placental pathology examination. For PTB, associations in the whole SPAH cohort and the requested subset were similar in direction and magnitude, except for acute inflammation, where the association was overestimated by 29% in the requested subset (ROR: 0.71, 95% CI: 0.52, 0.97) (Table 3). Similarly, in adjusted analyses, all grades of AI were significantly associated with lower odds of PTB, and at all grades the association was overestimated in the requested group compared to the full SPAH cohort by a range from 27% to 32%. Furthermore, adjusted analysis showed that any MVM and high-grade MVM were significantly associated with higher odds of PTB. With the presence of any MVM, the association was overestimated by 9% in the requested group, whereas the association with high-grade MVM was overestimated by 30%. While any FVM was not significantly associated with PTB, low-grade FVM was significantly associated with lower odds of PTB in the requested subset, an association that was overestimated by 12%, and not statistically significant in the full SPAH sample. CI was not significantly associated with PTB in adjusted models.

Of the 575 participants, 29 (5.0%) delivered an SGA infant; 20 of these had a delivering provider request placental pathology examination. For SGA infants, any MVM and high-grade MVM were significantly associated with increased odds of an SGA infant after covariate adjustment (Table 4). The magnitude of the impact of selection bias on the observed association was modest, with the ROR from the adjusted models indicating a 12% overestimate of the association in the requested subset which was attenuated to only 2% for high-grade MVM. While AI, CI, and FVM were not statistically significantly associated with SGA infants, the magnitudes of the RORs were generally consistent for the dichotomous and graded pathology variables.

TABLE 1 Demographics and clinical characteristics by pathology examination request.

	All placentas *N* = 575	Placental pathology NOT requested *N* = 288	Placental pathology requested *N* = 287	*p*-value
Maternal characteristics				
Age, years (mean (SD))	33.32 (5.63)	32.91 (5.43)	33.72 (5.79)	0.084
18–24 years	51 (8.9)	26 (9)	25 (9)	
25–34 years	286 (49.7)	154 (53)	132 (46)	
35-51 years	238 (41.4)	108 (38)	130 (45)	
Parity				0.672
Nulliparous	219 (38.1)	98 (34)	121 (42)	
Primiparous	201 (35.0)	109 (38)	92 (32)	
Multiparous	155 (26.9)	81 (28)	74 (26)	
Race				
Asian	69 (12.0)	36 (13)	33 (11)	0.712
Black or African American	102 (17.7)	54 (19)	48 (17)	0.526
White	365 (63.5)	186 (65)	179 (62)	0.582
Other	65 (11.3)	27 (9)	38 (13)	0.144
Hispanic ethnicity	141 (24.5)	62 (22)	79 (28)	0.095
Body Mass Index (mean(SD))	31.07 (7.97)	29.70 (6.98)	32.46 (8.67)	
<18.5	**3 (0.5)**	**1 (0)**	**2 (1)**	**<0.001**
18.5–24.9	**118 (20.5)**	**71 (25)**	**47 (16)**	
25–29.9	**166 (28.9)**	**100 (35)**	**66 (23)**	
30–34.9	**137 (23.8)**	**62 (22)**	**75 (26)**	
35+	**123 (21.4)**	**43 (15)**	**80 (28)**	
Mode of delivery, c-section	**169 (29.4)**	**61 (21)**	**108 (38)**	**<0.001**
Education Earned				0.234
High school Diploma or less	152 (26.4)	69 (24)	83 (29)	
Associate Degree	41 (7.1)	22 (8)	19 (7)	
Bachelor Degree	173 (30.1)	88 (31)	85 (30)	
Masters, Doctorate, or Professional Degree	209 (36.3)	109 (38)	100 (35)	
Hypertensive disorder	**133 (23.1)**	**30 (10)**	**103 (36)**	**<0.001**
Diabetes Mellitus	**121 (21.0)**	**28 (10)**	**93 (32)**	**<0.001**
Preterm delivery	**66 (11.5)**	**6 (2)**	**60 (21)**	**<0.001**
Chorioamnionitis	**33 (5.7)**	**6 (2)**	**27 (9)**	**<0.001**
Infant characteristics				
Gestational age, weeks (mean (SD))	**38.6 (2.0)**	**39.2 (1.0)**	**37.9 (2.5)**	**<0.001**
Birthweight (g) (mean(SD))	**3306 (612)**	**3434 (407)**	**3179 (742)**	**<0.001**
SGA infant	**29 (5.0)**	**9 (3)**	**20 (6)**	**0.036**
Infant sex				0.838
Female	256 (44.5)	127 (44)	129 (45)	
Male	319 (55.5)	161 (56)	158 (55)	
APGARS at 1 minute (mean(SD))	**8.05 (1.6)**	**8.46 (0.99)**	**7.64 (1.96)**	**<0.001**
APGARS at 5 minutes (mean(SD))	**8.72 (1.05)**	**8.89 (0.66)**	**8.54 (1.31)**	**<0.001**
ISCU admission	**70 (12.2)**	**9 (3)**	**61 (21)**	**<0.001**
Length of ISCU stay, days (mean (SD))	15.29 (18.16)	5.56 (6.78)	16.72 (18.89)	0.085

TABLE 2 Placental pathology distributions in the full sample and the requested subset.

	All placentas *N* = 575	Placental pathology NOT requested *N* = 288	Placental pathology requested *N* = 287	*p* value
Placental size				
Placental weight (mean (SD))	472 (100)	476 (86)	468 (113)	0.404
Small for gestational age	154 (27)	79 (27)	75 (26)	0.235
Acute Inflammation				
None	252 (44)	125 (43)	127 (44)	0.179
Low grade	240 (42)	134 (47)	106 (37)	
High grade	83 (14)	29 (10)	54 (19)	
Chronic inflammation				
None	259 (45)	132 (46)	127 (44)	0.821
Low grade	193 (34)	90 (31)	103 (36)	
High grade	123 (21)	66 (23)	57 (20)	
Fetal vascular malperfusion				
None	384 (67)	194 (67)	190 (66)	0.968
Low grade	149 (26)	71 (25)	78 (27)	
High grade	42 (7)	23 (8)	19 (7)	
Maternal vascular malperfusion				
None	**407 (71)**	**220 (76)**	**187 (65)**	**0.002**
Low grade	**101 (18)**	**44 (15)**	**57 (20)**	
High grade	**67 (12)**	**24 (8)**	**43 (15)**	

Note: Value represents *N*(%).

4 | DISCUSSION

This study leverages a prospective placental collection in a cohort of patients at a single institution, about one half of which the delivering provider requested a placental pathology examination, and compares the demographic, pathologic findings, and correlations with birth outcomes to the other half of which were only examined due to their inclusion in a research study. As such, this study offers a unique viewpoint into how the selection of placentas for a study can have an impact on the interpretation of associations with birth outcomes because we can compare a prospective sample to a pathology sample. Not surprisingly, our data indicate that patients whose placentas have a clinical request are more likely to have pregnancy complications, such as hypertensive disorders, diabetes mellitus, preterm delivery, and chorioamnionitis. These conditions are generally recommended indications for placental pathology examination [4, 15]. However, it is noteworthy that not all patients with these pregnancy complications have a placental requested; as seen in the Table 1, many placentas that met clinical indication were missed. Although recommendations and guidelines exist for placental examination, it can be difficult to adhere to them strictly in the clinical situation.

In terms of differences in placental pathologic findings between those patients with and without placental pathology request, somewhat surprisingly, only MVM prevalence differed significantly between the groups with more MVM and higher grade MVM in the requested group. MVM has a strong association with hypertensive disorders in pregnancy [16] and 36% of the patients in the requested group had a hypertensive disorder, which may contribute to the high prevalence of MVM in this group. Interestingly acute inflammation, chronic inflammation, and FVM were seen in both groups in nearly equivalent percentages, even with high-grade pathology present. This finding may reflect that these pathologic conditions are common in all placentas, and some studies have shown that these pathologies can be seen in up to one third of normal term pregnancies [17]; however, some placentas in the not-requested group met clinical criteria to warrant a placental pathology examination and should have been requested for review by the delivering provider.

Perhaps the most important part of our study was assessing how potential selection bias from use of a placental pathology requested sample, or "convenience" sample, selected based on adverse pregnancy outcomes, contributes to interpretations of a pathologic condition's contribution to PTB and SGA infant. Overall, the only

TABLE 3 Odds ratios and relative odds ratios for associations between grade of placental pathology and preterm birth in the full sample and the placental pathology requested subset.

	Unadjusted odds ratios			Adjusted odds ratios[a]		
	All placentas $N = 575$	Placental pathology requested $N = 287$	RORs	All placentas $N = 575$	Placental pathology requested $N = 287$	RORs
Presence of placental pathology						
Acute inflammation	**0.37 (0.22–0.64)**	**0.28 (0.15–0.52)**	0.76 (0.57, 1.01)	**0.38 (0.21–0.67)**	**0.27 (0.14–0.53)**	0.71 (0.52, 0.97)
Chronic inflammation	0.86 (0.51–1.43)	0.88 (0.50–1.57)	1.02 (0.80, 1.31)	0.81 (0.47–1.40)	0.84 (0.45–1.56)	1.04 (0.77, 1.40)
FVM	**0.50 (0.27–0.93)**	**0.47 (0.24–0.92)**	0.94 (0.72, 1.22)	0.59 (0.31–1.13)	0.58 (0.29–1.17)	0.98 (0.74, 1.30)
MVM	**2.97 (1.77–5.01)**	**2.92 (1.63–5.23)**	0.98 (0.75, 1.28)	**3.07 (1.76–5.35)**	**3.34 (1.74–6.38)**	1.09 (0.78, 1.52)
Grade of placental pathology						
Acute Inflammation						
None	*Reference*	*Reference*		*Reference*	*Reference*	
Low	**0.32 (0.18–0.60)**	**0.24 (0.12–0.50)**	0.75 (0.51, 1.10)	**0.34 (0.18–0.65)**	**0.23 (0.10–0.51)**	0.68 (0.44, 1.05)
High	0.52 (0.23–1.15)	**0.37 (0.16–0.84)**	0.70 (0.54, 0.90)	0.47 (0.20–1.11)	**0.35 (0.14–0.85)**	0.73 (0.54, 0.98)
Chronic Inflammation						
None	*Reference*	*Reference*		*Reference*	*Reference*	
Low	0.96 (0.54–1.70)	0.91 (0.48–1.71)	0.94 (0.71, 1.24)	0.99 (0.54–1.81)	0.93 (0.47–1.83)	0.94 (0.68, 1.29)
High	0.70 (0.34–1.43)	0.85 (0.39–1.85)	1.21 (0.90, 1.63)	0.55 (0.24–1.24)	0.67 (0.28–1.65)	1.23 (0.84, 1.80)
FVM						
None	*Reference*	*Reference*		*Reference*	*Reference*	
Low	**0.41 (0.20–0.86)**	**0.35 (0.16–0.78)**	0.85 (0.62, 1.17)	0.47 (0.22–1.01)	**0.42 (0.18–0.96)**	0.88 (0.62, 1.24)
High	0.86 (0.32–2.30)	1.09 (0.37–3.18)	1.26 (0.81, 1.95)	1.12 (0.40–3.10)	1.53 (0.49–4.71)	1.36 (0.84, 2.20)
MVM						
None	*Reference*	*Reference*		*Reference*	*Reference*	
Low	1.89 (0.97–3.69)	1.75 (0.84–3.67)	0.93 (0.68, 1.28)	1.86 (0.92–3.76)	1.86 (0.84–4.11)	1.00 (0.69, 1.45)
High	**4.99 (2.64–9.42)**	**5.15 (2.50–10.6)**	1.03 (0.73, 1.46)	**5.82 (2.89–11.7)**	**7.56 (3.23–17.7)**	1.30 (0.81, 2.10)

[a]Adjusted for BMI during the second trimester, c-section delivery, race and ethnicity, maternal age, and parity.

pathology that was associated with a statistically significant increased risk of PTB and SGA infant was MVM. We found that using a convenience sample does overestimate associations between MVM and PTB by 9% and MVM and SGA infants by 12%. Overestimation of PTB was even stronger for high-grade MVM (30%), potentially because of the strong association between HDP and PTB, and cases of HDP were over-represented in the requested group. The selection bias in estimating the association between SGA infant and high-grade MVM was actually attenuated compared to MVM as a dichotomous variable. However, it appears most of the overestimation was related to low-grade MVM, although this association was not statistically significant, though interpretation is limited by a relatively small prevalence of SGA infant.

Retrospective studies that use placental pathology samples submitted for placental pathology examinations represent the bulk of studies on placental pathology in the literature, as prospective collection of placentas is rarely included in clinical trials [18, 19] and can be difficult, time-consuming, and expensive. Furthermore, the lower quality of evidence from retrospective studies may be a reason for discounting findings that might be meaningful. Our results quantify the potential impact of selection bias on associations between placental pathology and APOs, and our findings can inform research leveraging retrospective pathology data. By quantifying selection bias, we found that the bias might not be as large as we anticipated. The ORs from the full sample and the requested subset did not differ in direction and the RORs indicated only mild-to-modest impact of selection bias on estimates of association between placental pathology and APOs. The selection bias in the requested group did not change the interpretation of the associations (positive or negative) with PTB and SGA infant, with only a modest impact on the magnitude.

TABLE 4 Odds ratios and relative odds ratios for associations between grade of placental pathology and small for gestational age infants in the full sample and the placental pathology requested subset.

	Unadjusted Odds Ratios			Adjusted Odds Ratios[a]		
	All placentas $N = 575$	Placental pathology requested $N = 287$	RORs	All placentas $N = 575$	Placental pathology requested $N = 287$	RORs
Presence of placental pathology						
Acute inflammation	1.29 (0.60–2.78)	1.52 (0.59–3.92)	1.18 (0.67, 2.07)	1.40 (0.57–3.45)	1.67 (0.55–5.10)	1.19 (0.62, 2.30)
Chronic inflammation	1.37 (0.63–2.95)	1.52 (0.59–3.92)	1.11 (0.63, 1.94)	1.16 (0.49–2.73)	1.67 (0.56–4.97)	1.44 (0.74, 2.82)
FVM	1.66 (0.78–3.53)	1.06 (0.41–2.75)	0.64 (0.36, 1.15)	1.76 (0.74–4.19)	0.98 (0.32–2.98)	0.56 (0.28, 1.13)
MVM	**3.73 (1.74–8.00)**	**4.91 (1.82–13.2)**	1.32 (0.70, 2.48)	**3.72 (1.55–8.95)**	**4.18 (1.36–12.9)**	1.12 (0.56, 2.26)
Grade of placental pathology						
Acute Inflammation						
None	*Reference*	*Reference*		*Reference*	*Reference*	
Low	1.46 (0.65–3.23)	1.79 (0.66–4.87)	1.23 (0.67, 2.25)	1.79 (0.71–4.52)	2.34 (0.73–7.49)	1.31 (0.65, 2.65)
High	0.82 (0.22–3.01)	1.01 (0.25–4.06)	1.23 (0.75, 2.01)	0.55 (0.11–2.75)	0.70 (0.13–3.92)	1.28 (0.69, 2.37)
Chronic Inflammation						
None	*Reference*	*Reference*		*Reference*	*Reference*	
Low	1.23 (0.51–2.96)	1.25 (0.42–3.69)	1.01 (0.54, 1.90)	0.99 (0.37–2.77)	1.49 (0.45–4.95)	1.50 (0.77, 2.92)
High	1.58 (0.62–4.04)	2.02 (0.65–6.30)	1.27 (0.66, 2.43)	1.45 (0.50–4.22)	2.09 (0.52–8.46)	1.44 (0.59, 3.53)
FVM						
None	*Reference*	*Reference*		*Reference*	*Reference*	
Low	1.65 (0.73–3.72)	1.14 (0.42–3.10)	0.69 (0.38, 1.25)	1.55 (0.59–4.04)	0.95 (0.29–3.17)	0.61 (0.29, 1.26)
High	1.76 (0.49–6.32)	0.76 (0.09–6.12)	0.43 (0.08, 2.25)	2.69 (0.70–10.3)	1.10 (0.13–9.38)	0.41 (0.08, 2.18)
MVM						
None	*Reference*	*Reference*		*Reference*	*Reference*	
Low	1.36 (0.43–4.30)	2.28 (0.62–8.37)	1.68 (0.92, 3.08)	1.54 (0.45–5.25)	2.26 (0.57–9.01)	1.47 (0.77, 2.80)
High	**8.07 (3.50–18.6)**	**9.14 (3.11–26.9)**	1.13 (0.57, 2.23)	**8.13 (3.07–21.5)**	**8.25 (2.32–29.4)**	1.02 (0.45, 2.30)

[a]Adjusted for BMI during the second trimester, c-section delivery, race and ethnicity, maternal age, and parity.

Limitations of this study include the use of data from a single study site and a single perinatal pathologist, thus limiting generalizability. The demographics and pregnancy outcomes in this study population were not significantly different from the larger delivering population at the study site, so we are internally valid to assess selection bias, but our population might not be representative of other delivery sites. Clinical indications for placental pathology review and provider understanding and discretion regarding requests for placental pathology examinations may also vary across institutions, limiting our generalizability. Selection into the SPAH study was not truly unselected or random, and potential unknown biases may be introduced, but importantly for this study, selection into the study occurred prior to 25 weeks gestation, and thus was not based on the presence or absence of an adverse pregnancy outcome. Further, the SPAH sample was recruited to reflect the sociodemographic characteristics of those delivering at the institution. Therefore, the whole SPAH sample can serve as an adequate representative sample to address this research question. Additionally, a potential limitation is that the perinatal pathologist conducting the examinations was not blinded to the clinical history provided in the cases where placental pathology was requested, as blinding was not part of the original SPAH study design. However, the use of standardized diagnostic protocols, such as used in the placental pathology examination for our study can minimize the subjectivity and increase diagnostic consistency without blinding [20, 21]. Lastly, we had a small number of SGA infants, resulting in imprecise estimates of associations between placental pathology and SGA infant, limiting our interpretation of the potential impact of selection bias.

Strengths of this analysis include the use of a large, diverse cohort with robust demographic and clinical information. Placentas were also reviewed by a single perinatal

pathologist following a standardized protocol regardless of reason or request for the placental examination. Collecting and examining placentas prospectively allowed us to be agnostic to the pregnancy outcome, which positioned us well to evaluate the selection bias related to clinical request. In addition to describing the selection bias, we quantify the impact, identifying a minimal to modest impact, with no change to the overall interpretation of results. Further, to the extent clinical indications for pathologic review and provider practices are similar at other institutions, our RORs can be applied to external studies to recover the estimate of association in the absence of selection bias. This can be done by dividing the observed estimate in the clinical pathology-based sample by the corresponding ROR [14], offering a simple method to correct for potential selection bias in other studies.

5 | CONCLUSION

In conclusion, MVM was the only pathology significantly associated with increased risk of APOs, and results generally suggest a modest impact of selection bias when using retrospective pathology samples. We additionally quantify the difference in APO associations driven by delivering provider request for examination, providing an estimate of the impact of selection bias using RORs. Overall, the impact and interpretation of associations between placental pathology and APOs were unchanged in the retrospective sub-sample.

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