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Original Research

A Cross Sectional Study of Second Trimester Sonographically Diagnosed Low-Lying Placenta and Associated Maternal and Neonatal Outcomes at Delivery

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Abstract

Background: The optimal management of patients diagnosed in the mid-gestation with a low-lying placenta (LLP) is controversial. We sought to determine the rate of adverse pregnancy outcomes with an initial diagnosis of LLP, and whether this was dependent on a follow up sonographic diagnosis of resolution or the initial placenta-to-internal os distance (P-IOD). **Methods**: A retrospective cross-sectional study of singleton pregnancies with a sonographically diagnosed LLP between 18–24 weeks' gestation (12/2010 to 7/2018) was conducted at a tertiary referral center in the U.S. Follow-up ultrasound examinations from the late second or early third trimester were reviewed. Maternal morbidity associated with blood loss, regardless of resolution of LLP was recorded and stratified by P-IOD at diagnosis. The LLP was considered resolved if the P-IOD was $\geq$2.0 cm by 34 weeks' gestation . Proportions of resolution, admissions for antepartum bleeding, preterm delivery, mode of delivery, neonatal morbidity and preterm delivery were obtained. Data was analyzed by comparing categorical variables via Chi-squared test, and continuous variables using Student *t*-test and analysis of variance (ANOVA). **Results**: Five hundred three pregnancies met inclusion criteria. All except two LLPs resolved by 34 weeks' gestation (99.6% resolution rate). There were 40 patients who did not have a follow up ultrasound. Overall rates of hemorrhage and blood transfusion were greater than the general population. The rate of maternal hemorrhage between resolved, unresolved, unknown groups, and initial P-IOD was not significantly different. The odds of admission for antepartum bleeding were significantly greater if the P-IOD was $<$0.5 cm. An increase in neonatal acidosis was found in the group with initial P-IOD $<$0.5 cm, despite 100% resolution at time of delivery. **Conclusions**: The diagnosis of an LLP at 18–24 weeks' gestation despite a high rate of resolution, is associated with an increased risk for maternal hemorrhage. LLP may be an independent risk factor for hemorrhage, regardless of the initial P-IOD or resolution. Clinicians and patients should be aware of this risk and prepared to manage adverse events.

Keywords: low lying placenta; hemorrhage; resolution; morbidity

1. Introduction

Placental related pregnancy complications such as obstetrical hemorrhage are common etiologies of global maternal and neonatal morbidity, mortality, and near misses. The reported incidence of a low-lying placenta (LLP) at 18–20 weeks' gestation is 1–9% in developed nations where second trimester ultrasound is routinely practiced [1,2]. Despite the high incidence, data regarding clinical implications of LLP in mid-gestation have been scarce and conflicting. Additionally, the term "low-lying placenta" has historically been used interchangeably with "marginal placenta previa", which has further complicated management guidelines [3–5]. The dearth of generalizable and reproducible evidence has led to controversy in the optimal approach to management of LLP.

Vintzileos in an expert opinion in 2015 proposed guidelines for management of LLPs diagnosed in mid gestation [3]. A repeat transvaginal ultrasound was recommended at 28–32 weeks' gestation. If the placental-internal os distance (P-IOD) was $>$2.0 cm from the internal cervical os, no further action was required, and vaginal delivery was deemed to be appropriate. If the P-IOD was $\leq$2.0 cm or less, a repeat ultrasound was recommended at 34–36 weeks' gestation. If the P-IOD was between 1–2 cm at that time, the recommendation was to obtain repeat ultrasounds every 1–2 weeks, monitoring for resolution. If the P-IOD was $\leq$1.0 cm at 34–36 weeks, the recommendation was to treat as a placenta previa with planned delivery by cesarean [3]. This recommendation was further discussed in a Clinical Expert Series published by American College of Obstetrics and Gynecology (ACOG) in 2015 and seems to be the general recommendation and practice of most organizations [4]. However, other studies have suggested this may be too conservative [6]. Per the Society of Obstetricians and Gynaecologists of Canada (SOGC) 2020 guidelines, repeat ultrasound is recommended at $\geq$32 weeks, and a trial of labor is permissible for a P-IOD between 1.1 and 2.0 cm, but may be considered if P-IOD $\leq$1.0 cm in select cases [7].

Several studies have demonstrated that the vast majority, 95–99.5%, of strictly defined LLPs (distal placental edge $<$2.0 cm from, though not overlapping, the inter-

nal cervical os) diagnosed at mid-trimester ultrasound ultimately resolve [1,2,8–11]. This is reassuring and may demonstrate that follow up ultrasounds and monitoring for resolution is unnecessary. A recent study concluded that lowering the P-IOD from 2.0, down to 0.5 cm as a threshold for obtaining a follow up ultrasound would decrease the number of follow-up ultrasounds, without missing high risk patients [12].

There also continues to be concern regarding morbidity and adverse outcomes associated with LLP. There have been few studies looking at the finding of a mid-gestation LLP as an independent risk factor for adverse outcomes, which have shown that the most significant concern is increased blood loss or postpartum hemorrhage [9,10,13–15]. Interestingly, even in the setting of a persistent LLP, the mode of delivery does not appear to affect the rate of postpartum hemorrhage or blood loss [6,13,16]. The objective of this study was to determine if an initial diagnosis of LLP affected the rate of adverse pregnancy outcomes and to determine the rate of LLP resolution.

2. Materials and Methods

This is a retrospective cross sectional study of patients with singleton pregnancies with a sonographically diagnosed LLP between 18 w 0 d and 24 w 0 d gestation from an American Institute of Ultrasound in Medicine (AIUM) accredited single institution, from December 2010 through July 2018. The hospital is a tertiary referral center located in the Midwest United States, with approximately 4500 annual deliveries during the study period. Obstetrical care is provided by private attending obstetricians, midwifes, faculty attending physicians and resident physicians. All ultrasounds were performed by sonographers with American Registry for Diagnostic Medical Sonography (ADRMS) registration in obstetrical ultrasound and read by one of six board-certified Maternal-Fetal Medicine specialists. The ultrasound equipment consisted of General Electric Voluson E8 (GE Healthcare, Chicago, IL, USA) and Siemens S2000 (Siemens Healthcare, Erlangen, Germany). Inclusion criteria were all singleton pregnancies with a diagnosed LLP between 18–24 weeks' gestation. Exclusion criteria consisted of multiple gestations, major congenital anomalies, placenta previa, vasa previa, suspected morbidly adherent placenta, known maternal coagulopathy, intrauterine fetal death, inability to clearly image the inferior placental edge or internal cervical os on transabdominal ultrasound and declined transvaginal ultrasound, and women who did not deliver at our institution.

In accordance with AIUM and ACOG guidelines, the placental location, appearance, and relationship to the internal cervical os were recorded on digital media [17]. The placental location was determined by transabdominal ultrasound (TAUS) in the absence of a lower uterine segment contraction defined as a transient focal thickening of the myometrium. The cervix was identified in the mid-sagittal plane by locating the echolucent or echodense endocervical canal and the proximal internal cervical os. If the inferior edge of the placenta was unable to be clearly visualized, or if the internal cervical os could not be identified, transvaginal ultrasound (TVUS) was then performed with an empty bladder. The P-IOD was measured from the inferior placental edge to the internal cervical os. LLP was diagnosed when the inferior placental edge was less than 2.0 cm from the internal cervical os, but not overlying the cervical os. The cervical length was measured in all cases.

Patients with the diagnosis of LLP had a follow-up ultrasound scheduled at 28–32 weeks. The placental location and LLP were assessed earlier if a repeat ultrasound was performed for an alternative indication, or later if one was not performed at the recommended gestational age.

The stored digital images from all ultrasounds were reviewed by a single author (BLC). The patients were divided into three groups based upon the resolution outcome at the follow-up ultrasound (Fig. 1).

All deliveries were performed at a single institution in Dayton, OH, USA, a regional perinatal tertiary referral center. The ultrasound data base and electronic medical record were used to collect demographic, placental and delivery data. Parity was counted for deliveries that occurred at $\geq$20 weeks' gestation (i.e., abortions were not counted as a parous event), and expressed as a continuous variable (mean $\pm$ Std. Deviation). Prior uterine surgery was defined as having a prior cesarean delivery or prior gynecological surgery involving the uterine corpus. The primary outcome was morbidity related to blood loss, regardless of resolution and stratified by initial P-IOD at diagnosis. Blood loss was compared between the initial P-IOD stratified by three distances: 0 to 0.49 cm, 0.5 to 0.99 cm, and 1.0 to 2.0 cm.

Morbidity from blood loss was described by the following characteristics: postpartum hemorrhage (PPH) defined as estimated blood loss (EBL) $>$500 mL in a vaginal delivery, EBL $>$1000 mL in a cesarean delivery, undiagnosed postpartum hemorrhage (UPPH) defined as a drop in antepartum to postpartum hemoglobin $>$3 g/dL, or requiring a blood transfusion or surgical procedure such as manual or instrumented removal of the placenta, or hysterectomy (all dichotomous variables). If EBL was not recorded or postpartum hemoglobin not obtained, they were classified normal. Secondary outcomes included rate of LLP resolution, rate of admissions for antepartum bleeding, mode of delivery, rate of preterm delivery, and neonatal morbidity including umbilical artery pH $<$7.15 and neonatal hemoglobin $<$13 g/dL. Only patients with documented values of umbilical artery pH and neonatal hemoglobin were included in those respective analyses. Additionally, the effects of prior uterine surgery and current tobacco use on resolution of LLP were analyzed. Two hundred fifty-one patients with LLP were required with 80% power and a type I error rate of 0.05% to detect a three-fold increase in maternal hemorrhage.

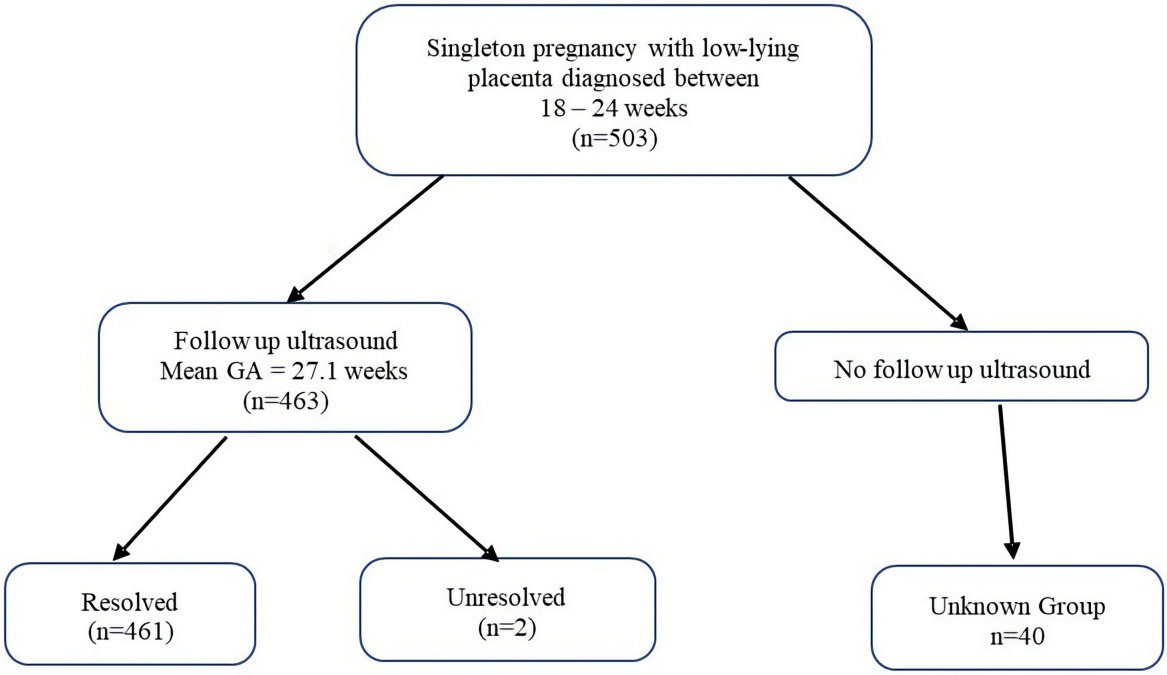

Fig. 1. Groupings based upon resolution outcome at follow-up ultrasound. If the placenta-to-internal os distance (P-IOD) was 2.0 cm or greater on any subsequent ultrasound, the low-lying placenta (LLP) was considered resolved (n = 461) and no further investigation was recommended. The second group, "unknown resolution" (n = 40), was when the P-IOD was less than 2.0 cm at the initial ultrasound and did not have a follow up ultrasound. The third group, "unresolved" (n = 2), was when the P-IOD was less than 2.0 cm at 34 weeks' or later. Patients with unknown resolution were excluded from the analysis of the resolution rate, though were included in overall outcome analyses. GA, gestational age.

Statistical analyses consisted of comparing categorical variables via Chi-squared test, and continuous variables using Student *t*-test and analysis of variance (ANOVA). A p value of < 0.05 was considered significant. Additionally, receiver operating characteristic (ROC) curves were designed to assess for diagnostic ability of specific characteristics to predict resolution or maternal morbidity. Briefly, the ROC curves were constructed with the I-POD or LLP resolution as the independent variables, and the individual maternal morbidities as the dependent variable. The ROC curve was compared to the 45-degree non-discriminatory line for diagnostic significance, with $p < 0.05$. All patients were included in the ROC curve analyses. Statistical analyses were performed using SPSS Version 25.0 (IBM Corp., Armonk, NY, USA) (ROC curves, and comparisons) and Microsoft Excel (Microsoft 365 Apps for Windows, Version 2308, Microsoft Corporation, Redmond, WA, USA) (descriptive statistics).

3. Results

Five hundred three patients meeting the inclusion criteria were found to have an LLP between 18–24 weeks' gestation. For the entire sample, the mean maternal age was 29.4 $\pm$ 6 years and the mean gestational age at diagnosis of LLP was 20.0 $\pm$ 1 weeks'. There was no significant difference found in age, body mass index (BMI), race, parity, neonatal weight, gestational age at diagnosis, resolution, or delivery, placental position, or cervical length at time of diagnosis of LLP based on the initial P-IOD, or between resolved groups (Table 1). There also was no difference between current tobacco use or history of uterine surgery between groups (Table 1). Confirmation of the diagnosis of LLP in the mid-trimester by transvaginal ultrasound was necessary in 199/503 (39.6%) patients.

Follow up ultrasounds were performed in 463/503 (92.0%) patients, of which 461/463 (99.6%) resolved. The average gestational age at the time of the follow up ultrasound was 27.1 weeks, which did not differ between P-IOD measurements. Given that there were only 2 unresolved patients, analysis of the unresolved group was not practical.

Out of the 503 patients evaluated, 21 (4.2%) experienced a PPH, 59 (11.7%) had UPPH, and 13 (2.6%) required a blood transfusion. The overall mean blood loss was 430 $\pm$ 206 mL with an average drop in hemoglobin from antepartum to postpartum of 1.87 $\pm$ 1.1 g/dL. There was not a significant difference in the primary outcome maternal morbidity based on the initial P-IOD, or LLP resolution status (Table 2). Three patients required a manual removal of the placenta for post-partum hemorrhage. These outcomes were not affected by P-IOD or resolution of LLP (Table 2). There were no hysterectomies.

Table 1. Patient demographics and history based upon P-IOD and resolution status.

	Initial P-IOD measurement				LLP resolution status			
	0–0.49 cm	0.5–0.99 cm	1.0–2.0 cm	*p* value	Resolved	Unresolved	Unknown	*p* value
	(n = 40)	(n = 77)	(n = 386)		(n = 461)	(n = 2)	(n = 40)	
Age (years)	31.1 (±6)	29.1 (±6)	29.2 (±6)	0.585	29.3 (±6)	32.8 (±6)	31.0 (±4)	0.406
BMI (kg/m^2)	29.6 (±8)	29.7 (±8)	30.3 (±8)	0.762	30.2 (±8)	24.0 (±5)	29.7 (±8)	0.167
Caucasian	29 (72.5)	62 (80.5)	301 (78.0)	0.698	355 (77.0)	2 (100)	34 (85)	0.436
Posterior placenta	23 (57.5)	53 (68.8)	255 (66.1)	0.708	301 (65.3)	1 (50)	29 (72.5)	0.996
Tobacco use	11 (27.5)	13 (16.9)	107 (27.7)	0.144	125 (27.1)	1 (50)	14 (35)	0.285
Prior uterine surgery	9 (22.5)	16 (20.8)	68 (17.6)	0.619	80 (17.4)	1 (50)	11 (27.5)	0.225
Parity	2.18 (±2)	1.94 (±2)	2.11 (±2)	0.502	2.06 (±2)	3.00 (±1)	2.50 (±2)	0.574
GA at diagnosis (weeks)	19.9 (±1)	20.1 (±1)	19.9 (±1)	0.375	19.9 (±1)	19.9 (±1)	20.2 (±1)	0.559
Cervical length (cm)	3.73 (±1)	3.80 (±1)	3.83 (±1)	0.659	3.83 (±1)	4.63 (±1)	3.82 (±1)	0.176

Values are mean of group (± standard deviation) or n (%); BMI, body mass index. All comparisons were non-significant ($p \geq 0.05$).

Table 2. Maternal morbidity related to blood loss.

	Initial P-IOD measurement			LLP resolution status		
	0–0.49 cm	0.5–0.99 cm	1.0–2.0 cm	Resolved	Unresolved	Unknown
	(n = 40)	(n = 77)	(n = 386)	(n = 461)	(n = 2)	(n = 40)
GA at delivery (weeks)	38.7 (±2)	38.8 (±2)	38.7 (±2)	38.7 (±2)	39.2 (±1)	38.4 (±3)
PPH	3 (7.5)	2 (2.6)	16 (4.1)	20 (4.3)	0	1 (2.5)
UPPH	7 (17.5)	8 (10.3)	44 (11.3)	56 (12.1)	1 (50.0)	2 (5.0)
Blood transfusion	2 (5.0)	1 (1.3)	10 (2.6)	12 (2.6)	0	1 (2.5)
Manual removal of the placenta	2 (5.0)	1 (1.3)	0	3 (0.7)	0	0

Values are mean of group (± standard deviation) or n (%). PPH, postpartum hemorrhage defined as estimated blood loss (EBL) >500 mL in a vaginal delivery, or EBL >1000 mL in a cesarean delivery; UPPH, undiagnosed postpartum hemorrhage, defined as a drop in antepartum to postpartum hemoglobin >3 g/dL. Comparisons were between initial P-IOD distances and between resolution status. All comparisons were non-significant ($p \geq 0.05$).

There were 24/503 (4.8%) antepartum admissions for vaginal bleeding. There was a statistically significant difference in the number of admissions for antepartum bleeding based in the initial P-IOD, Table 3. The odds of being admitted for antepartum bleeding was significantly greater if the P-IOD was <0.5 cm, compared to a P-IOD of 0.5 cm or greater (odds ratio = 5.57, 95% confidence interval (95% CI) = 2.16–14.37). The rate of antepartum admissions was not significantly different based upon resolution status. There was a difference seen in neonatal acidosis. When the initial P-IOD was <0.5 cm, the rate of umbilical arterial pH <7.15 was significantly greater than if the P-IOD was greater than or equal to 0.5 cm (29.6% *vs* 10.1%, odds ratio = 3.96, 95% CI = 1.57–10.02) (Table 3). There was no significant difference noted in the remaining secondary outcomes, including mode of delivery, preterm birth rate or neonatal anemia. The overall cesarean section rate was 31.4%, 5 of which were performed due to antenatal bleeding, with the remainder being for unrelated indications. Of the 5 cesarean sections performed for antenatal bleeding, all had an initial P-IOD of 1.0 cm or more and 4 out of 5 had resolved on the follow up ultrasound, with 1 unknown. Due to the overall lack of significance in factors affecting resolution as well as primary outcomes, the ROC curves that were created were not of significance and therefore not included.

4. Discussion

Almost all (99.6%) LLPs diagnosed at mid-gestation resolve by 34 weeks' gestation. Regardless of resolution or the P-IOD, patients with a mid-gestation diagnosis of LLP had higher rates of maternal morbidity related to bleeding than what is seen in the general population (4.2% PPH, 11.7% UPPH, and 2.6% blood transfusion). Also, when the P-IOD was <0.5 cm there was a greater number of antepartum admissions for bleeding, and a greater number of cases of umbilical cord arterial acidosis at birth. Cesarean delivery rate was not affected by the presence of an LLP.

The rate of resolution is consistent with previous literature, documenting between 95–99% [1,2,10,11,14,18]. The rate of PPH was higher than what has been reported based on data from the Nationwide Inpatient Sample (NIS), the largest publicly available inpatient database in the U.S. (4.2% *vs* 2.9%) [19–23]. The postpartum transfusion rate was 2.6% which appears to be almost two-fold the documented range of national postpartum transfusion rate (0.3% to 1.7%) [20,24–26]. UPPH, defined here as a change in

Table 3. Secondary outcomes.

	Initial P-IOD measurement			LLP resolution status		
	0–0.49 cm	0.5–0.99 cm	1.0–2.0 cm	Resolved	Unresolved	Unknown
	(n = 40)	(n = 77)	(n = 386)	(n = 461)	(n = 2)	(n = 40)
Antepartum admissions for bleeding	7/40 (17.5)*	3/77 (4.0)	14/386 (3.6)	22/461 (4.8)	0/2	2/40 (5.0)
Vaginal delivery	25/40 (62.5)	53/77 (68.8)	267/386 (69.2)	319/461 (69.2)	1/2 (50.0)	25/40 (62.5)
Cesarean delivery	15/40 (37.5)	24/77 (31.2)	119/386 (30.8)	142/461 (30.8)	1/2 (50.0)	15/40 (37.5)
UA pH <7.15†	8/27 (29.6)*	3/43 (7.0)	21/207 (10.1)	32/268 (11.9)	0/2	0/9
Neonatal Hgb <13 g/dL†	0/6	1/13 (7.7)	3/53 (5.7)	1/71 (1.4)	0/2	0/1
Preterm birth	6/40 (15.0)	12/77 (15.6)	40/386 (10.4)	54/461 (11.7)	0/2	4/40 (10.0)

Values are n (%). UA pH, umbilical arterial cord pH at delivery; Hgb, hemoglobin. †Not all patients had umbilical artery blood gas or neonatal hemoglobin measurements, n is denoted in the denominator. Comparisons were between initial P-IOD distances and between resolution status. All comparisons were non-significant except where noted: *p value < 0.05.

hemoglobin from antepartum to postpartum of >3 g/dL, as described elsewhere, was higher than previously documented (11.7% *vs* 3.8%) [27,28]. The increase in admissions for antepartum bleeding when the P-IOD was <0.5 cm, is contrary to the findings reported by Ogueh, who reported no increase in antepartum bleeding [15]. Antepartum bleeding has several etiologies, including but not limited to placental abruption, preterm labor, cervicitis, or preterm premature rupture of membranes, therefore this finding would need to be confirmed. The overall rate of neonatal acidosis in our population was higher compared to previously documented rates in term neonates (11.5% *vs* <3%) [3,29–31]. The finding of increased neonatal acidosis appears to be a novel finding, though additional research is warranted to further evaluate this association.

We speculate the observed higher rate of obstetrical hemorrhage and blood transfusion, antepartum hemorrhage, and umbilical cord acidosis may have a common etiology due to defective placental implantation and function. The lower uterine segment is thinner, with less blood flow compared to the contractile portion of the uterine corpus. This may be confounded when the placenta lies closer to the internal cervical os (e.g., <0.5 cm) where the proximity may increase the risk for clinically significant antenatal bleeding requiring hospitalization, and a greater proportion of the placenta is implanted over the lower uterine segment. Our data suggests the finding of an LLP in the second trimester is pathological and patients are at increased the risk for hemorrhage and fetal acidosis.

The strengths of this study include the large sample size obtained in a setting where evaluation of the placental location with respect to the cervix was the routine. As such, it was pragmatic compared to a study specifically focusing on evaluation of the placental location. For the study, all ultrasounds were reviewed by a single observer, decreasing inter-observer variability. Blood loss was quantified objectively with pre- and post-partum hemoglobin assessment, in addition to the subjective EBL documented by providers. Limitations of this study include the retrospective study design which is a lower level of evidence compared to a prospective study. Furthermore, the diagnosis of LLP and P-IOD was not universally confirmed with transvaginal ultrasound if able to be clearly visualized with transabdominal ultrasound, which may increase or decrease the diagnosis of LLP. Lastly, the ultrasounds were performed by one of several available sonographers, though all American Registry for Diagnostic Medical Sonographers (ARDMS) registered, and read by one of six Maternal-Fetal Medicine specialists, providing the opportunity for interobserver variation.

5. Conclusions

This research suggests that the presence of an LLP results in an inherent increase in maternal morbidity, which does not change despite P-IOD or resolution. In cases where both vasa previa and morbidly adherent placenta are confidently ruled out at the initial ultrasound, a follow-up ultrasound evaluation solely for LLP may be redundant. Providers may safely choose to forgo a follow up ultrasound, simply note the increased risk for maternal morbidity, and provide patients with precautions.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

BLC contributed to the conception, design, acquisition, analysis, and interpretation of data, and was involved in drafting and critically reviewing the manuscript. DSM contributed to the conception, design, interpretation of data, and was involved in drafting and critically reviewing the manuscript. RAM contributed to the design, analysis, and interpretation of data, and was involved in drafting and critically reviewing the manuscript. Each author has participated sufficiently in the work and takes responsibility for appropriate portions of the content; and agrees to be accountable for all aspects of the work in ensuring that ques-

tions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

An exemption for informed consent was obtained from the institutional review board for this study since it was retrospective and only de-identified data were utilized. The Wright State University Institutional Review Board reviewed and determined this study was exempt from IRB review (WSU IRB #06611, February 18, 2019).

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Conflict of Interest

The authors declare no conflict of interest.

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