Influence of antepartum hemorrhage on placenta previa: A multi-center, retrospective cohort study

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Abstract

BACKGROUND

Placenta previa can be a serious, life-threatening obstetric complication that causes painless but potentially catastrophic bleeding. It is unclear as to whether the frequency of antepartum hemorrhage (APH) relative to the specific gestational week in placenta previa will lead to negative perinatal outcomes. The purpose of the present study was to determine the relationship between APH and gestational week number, and to ascertain the different perinatal outcomes in women with placenta previa.

METHODS

This was a multi-center, retrospective study in which we enrolled all women with placenta previa between October of 2015 and September of 2018. Patients with placenta previa were divided into two groups: women with APH and women without APH.

RESULTS

A total of 247 patients were included in this study: 121 women with APH and 126 women without. The incidence of APH was 49.0% (121/247). The mean bleeding frequency was 2.2 ± 1.3 (mean ± SD), with the majority having experienced a one-time bleeding episode (36.4%, 44/121), followed by 26.4% with 2 episodes (32/121), and 23.1% with 3 (28/121). The APH was distinct in every gestational-week category, with bleeding occurring at 31.4 ± 3.3 weeks, ranging from 24 to 37 gestational weeks. The incidence of bleeding varied from 2.6–14.6%, with the highest incidence at 32 gestational weeks. Patients categorized as having complete placental coverage included a greater number of women experiencing bleeding than women who did not bleed (72.9% vs 47.4%, $P < 0.001$), indicating that a complete placenta was an independent risk factor for APH (odds rations [OR], 4.17; 95% confidence interval [CI], 1.805–9.634). In addition, although APH did not augment the rates of hysterectomy (6.6% vs 7.1%, $P = 0.869$), it was associated with critical neonatal outcomes that included lower weight, lower Apgar score at 1 minute, preterm age, and more frequent neonatal intensive care unit admissions ($P < 0.05$).

CONCLUSIONS

The gestational week and frequency of each APH varied in patients with placenta previa and might result in an increase in adverse maternal and neonatal outcomes. The 32nd gestational week appeared to be the most precarious time—exhibiting the highest incidence of bleeding—and we consider complete placenta previa to be an independent risk factor for APH.

Background:

Placenta previa—a condition where the placenta lies directly over the internal os[1]—is a serious obstetric complication that leads to increased maternal and neonatal mortality and morbidity; its incidence is reported to vary between 0.15% and 0.91%. [2–6] Clinically, placenta previa presents as recurrent painless vaginal bleeding in the antenatal period and massive hemorrhage during cesarean delivery (CD) and postoperatively. Antepartum hemorrhage (APH) is defined as bleeding from or into the genital tract that occurs from 24^{+0} weeks of pregnancy and prior to the birth of the baby.[7] However, not all patients with placenta previa encounter APH, and some may not experience any bleeding during the entire prenatal period. It is thus currently unclear as to which risk factors contribute to APH or at which gestational week bleeding occurs. To our knowledge, there are no extant studies in the literature that describe the relationship between APH and gestational week.

Given the importance yet paucity of the existing literature on this topic, the aims of the current study were to identify the following in placenta previa patients: 1) the relationship between APH and gestational week, 2) risk factors for APH, and 3) whether patients with APH developed more severe adverse perinatal outcomes. This knowledge will help to improve the antenatal management of placenta previa and optimize prophylactic measures to ameliorate outcomes.

Methods:

The present investigation was a multi-center, retrospective study approved by the Institutional Review Board at Partners Healthcare System (PHS) (Protocol#2019P000028). We collected all patient delivery data between October of 2015 and September of 2018 within PHS; this includes 7 different hospitals, 2 of which are large, tertiary, academic medical centers. The total number of deliveries during this period was 39,945, including 12,884 cesarean deliveries (32.3%) and 27,061 vaginal deliveries (67.7%). We sought patients in the PHS using the indication of placenta previa for “cesarean section” or “cesarean delivery”, and found 259 patients who met this criterion. At our institution, whenever placenta previa was identified by ultrasonography in the second trimester, a follow-up ultrasonographic examination was performed at 32–34 weeks of gestation to evaluate the relationship between the placenta and the cervix. All included cases were consistent with the ultrasonographic image produced before CD.

To avoid data bias in maternal and newborn outcomes, we excluded patients with multiple pregnancies (n = 8), stillbirths (n = 1), or delivery at less than 24 weeks of gestational age (n = 3). A total of 247 patients were ultimately included in our study.

Demographic data were collected from electronic medical records (EMR) and included maternal age, gravidity, parity, body mass index (BMI), smoking history, in vitro fertilization (IVF) history, prior number of CDs, history of CDs, and duration of the CD interval. The interval duration depicted the interval between the most recent CD and the current delivery. Gestational week was either calculated using the date of the last menstrual period or estimated from the first-trimester ultrasonographic measurements. We obtained placental location and classification from the last ultrasonographic report prior to delivery, and this was validated during CD. The placenta was classified as either complete, incomplete (marginal or partial), or

low lying. Placenta accreta was recorded from patient surgical records and confirmed by pathologic diagnosis. We also located maternal and neonatal outcomes in the surgical records as well as in anesthesia and neonatal records. The intraoperative variable of “total blood product” represented the sum total (units) of any blood product administered during the operative period, including packed red blood cells (PRBC), cell salvage, fresh frozen plasma (FFP), platelets, cryoprecipitate, and albumin. We defined postpartum hemorrhage (PPH) as an estimated blood loss (EBL) over 1000 ml. Hemoglobin (HGB) concentration and hematocrit (HCT) percentage during the first trimester, pre-operation, and postoperatively were procured from laboratory results found in the EMR.

All vaginal bleeding was recorded in our data, including the number of bleeding episodes and specific gestational week when bleeding occurred. Persistent bleeding was recorded once at the beginning of bleeding; however, if the patient experienced an interval without bleeding for more than 1 week, then the next bleeding was considered a second bleeding incident. Repeated bleeding was recorded several times according to the number of bleeding episodes. All hemorrhages were recorded, including those that occurred during inpatient and outpatient visits; however, bleeding caused by labor was not included. We observed no bleeding caused by neoplasm, infection, trauma, or iatrogenesis in any of our cases. There was also no bleeding due to vasa previa or placental abruption. The amount of bleeding was not included in our data as the majority was not quantified. All included cases met the recommendations and guidelines for data collection and analysis for APH in placenta previa.[8]

We conducted our statistical analysis using the Statistical Package for Social Sciences (SPSS) software, version 23.0. Continuous variables are presented as means ± 1 standard deviation (SD) or medians with an inter-quartile range, and we made comparisons between placenta previa with or without APH using the independent-sample *t* test or non-parametric Mann-Whitney U test depending upon normality of the data distribution. Categorical variables are shown as counts and percentages, and the differences were assessed using Chi-squared analysis; Fisher’s exact-probability test was used when appropriate. A value of $P < 0.05$ was considered statistically significant. We used logistic regression to study the independent risk factors for APH: the dependent variable was APH, and age, gravidity, parity, BMI, history of CD, number of prior CDs, duration of CD interval, placental location, and placental classification all served as covariates, with $P < 0.01$ representing a significant difference. Results are reported using odds ratios (OR) and 95% confidence intervals (CI). We used a Kaplan-Meier survival curve to show placenta previa patients with or without APH who remained undelivered at each gestational week.

Results:

The prevalence of placenta previa in our study was 0.65% (259/39945), and the mean number of gestational weeks at delivery was 36.4 ± 0.5. We identified 247 patients who underwent CD for placenta previa: 17 of these underwent a hysterectomy (6.9%, 17/247), 7 were treated with a uterine balloon (2.8%, 7/247), 3 underwent bilateral uterine artery embolization (1.2%, 3/247), and 7 patients received ureteral stents (2.8%, 7/247).

The incidence of APH in placenta previa was 49.0% (121/247). The mean number of bleeding episodes was 2.2 ± 1.3. While most experienced a one-time bleeding episode (36.4%, 44/121), 26.4% had 2 (32/121), 23.1% had 3 (28/121), 9.1% had 4 (11/121), 1.7% had 5 (2/121), 2.5% had 6 (3/121), and 0.8% had 7 hemorrhagic episodes (1/121). With respect to all bleeding patients, the week in which bleeding occurred was 31.4 ± 3.3, with the highest incidence of bleeding occurring at 32 weeks of gestation at a rate of 14.6% (Fig. 1). No bleeding occurred after the 38th gestational week, as most placenta previa patients underwent elective CD at 36–37 weeks. If there was a history of bleeding, CD was performed before 37 weeks. The difference between bleeding in the second trimester (21.9%, 51/233) and bleeding in the third trimester (78.1%, 182/233) was statistically significant ($\chi^2 = 73.625$, $P = 0.000$).

Although we did not observe any statistical differences in the demographic characteristics between patients with or without APH (Table 1) ($P > 0.05$), there was a significant difference in placental classification ($P < 0.05$), particularly with respect to the complete-placenta category, where the bleeding group exhibited a higher prevalence than the non-bleeding group (72.9% vs 47.4%). Having complete-placental coverage was thus an independent risk factor for APH in placenta previa patients (OR, 4.17; 95% CI, 1.805–9.634).

Table 1
Demographic and obstetric characteristics of the study

	Without APH	With APH	
	(n = 126)	(n = 121)	P value
Age (years), mean ± SD	34.7 ± 4.6	34.9 ± 4.2	0.893
Gravidity, median (range)	2 (2–4)	3 (2–4)	0.172
Parity, median (range)	1 (0–2)	1 (1–2)	0.116
BMI (kg/m^2), mean ± SD	29.7 ± 5.2	29.1 ± 5.7	0.182
Smoking, n (%)	24 (19.0)	19 (15.7)	0.488
IVF, n (%)	31 (24.8)	33 (27.3)	0.659
Prior CD number, median (range)	0 (0–1)	0 (0–0)	0.217
CD history, n (%)	34 (27.0)	25 (20.7)	0.244
CD interval (year), median (range)	2.7 ± 4.3	2.9 ± 3.9	0.239
Fetal presentation, n (%)			0.590
vertex	110 (87.3)	100 (82.6)	
breech	9 (7.1)	12 (9.9)	
transverse	7 (5.6)	9 (7.4)	
GBS infection, n (%)	99 (88.4)	102 (87.9)	0.914

APH, antepartum hemorrhage. BMI, body mass index. IVF, in vitro fertilization. CD, cesarean delivery. GBS, group B streptococcus.

The gestational week in which delivery occurred for patients without APH was much later than for patients with hemorrhage (37.1 ± 1.6 vs 35.6 ± 1.9, p = 0.000). Figure 2 depicts a Kaplan-Meier curve of the proportion of placenta previa patients with or without APH who remained undelivered at each gestational week, showing that 89.1% delivered beyond 34 weeks of gestation and that 53% delivered beyond 37 weeks of gestation.

In addition to gestational week, we observed significant differences between the 2 groups with regard to maternal outcomes including length of hospital stay, first trimester and pre-operative levels of HGB and HCT, emergent CD, blood transfusion rate, total blood product, general anesthesia (GA), and American Society of Anesthesiologists (ASA) physical status classification (P < 0.05). There were no differences in placenta accreta (11.1% vs 13.2%, p = 0.611) or other parameters, including anesthesia time, procedural duration, total fluid infusion, EBL, PPH, hysterectomy, or intensive care unit (ICU) admission (P > 0.05) (Table 2).

Table 2
Placental characteristics and maternal outcomes of cesarean delivery among parturients with placenta previa

	Without APH	With APH	
	(n = 126)	(n = 121)	P value
ASA status, n (%)			0.049
1	13 (10.3)	6 (5.0)	
2	95 (75.4)	85 (70.2)	
3–4	18 (14.3)	30 (24.8)	
Placental location, n (%)			1.000
Anterior	31 (26.7)	30 (25.9)	
Posterior	66 (56.9)	67 (57.8)	
Lateral	5 (4.3)	5 (4.3)	
Anterior + posterior	14 (12.1)	14 (12.1)	
Placental classification, n (%)			0.000
Complete	55 (47.4)	86 (72.9)	
Incomplete	37 (31.9)	23 (19.0)	
Low lying	24 (20.7)	9 (7.6)	
Placenta accreta, n (%)	14 (11.1)	16 (13.2)	0.611
Emergent CD, n (%)	15 (11.9)	66 (54.5)	0.000
Duration of procedure (min), mean ± SD	63.6 ± 48.0	66.8 ± 45.9	0.801
Anesthetic type, n (%)			0.024
General anesthesia (GA)	1 (0.8)	9 (7.4)	
Neuraxial anesthesia (NA)	121 (96.0)	108 (89.3)	
NA converted to GA	4 (3.2)	4 (3.3)	
Anesthesia time (min), mean ± SD	123.8 ± 78.1	136.9 ± 116.0	0.114
EBL (ml), median (range)	800 (775–1000)	900 (800–1215)	0.109
PRBC product (ml), mean ± SD	1112.7 ± 812.4	863.0 ± 898.7	0.269

APH, antepartum hemorrhage. ASA, the American Sociological Association. CD, cesarean delivery. EBL, estimated blood loss. PRBC, packed red blood cells. HGB, hemoglobin. HCT, hematocrit. PPH, postpartum hemorrhage. ICU, intensive care unit.

	Without APH	With APH	
All blood products (ml), mean ± SD	238.3 ± 1046.4	297.5 ± 1170.4	0.045
Blood transfusion, n (%)	12 (9.5)	23 (19.0)	0.033
Total fluid infusion (ml), median (range)	1600 (1000–2000)	1500 (1100–2225)	0.395
HGB (g/dl), mean ± SD			
First trimester	12.4 ± 1.1	12.0 ± 1.2	0.022
Pre-operation	11.8 ± 1.3	11.2 ± 1.3	0.000
Post-operation	9.9 ± 2.5	9.5 ± 1.4	0.207
HCT (%), mean ± SD			
First trimester	36.8 ± 3.0	35.6 ± 3.6	0.012
Pre-operation	35.0 ± 3.1	33.3 ± 3.8	0.001
Post-operation	28.9 ± 3.7	28.4 ± 4.2	0.245
PPH, n (%)	46 (36.5)	56 (46.3)	0.119
Hysterectomy, n (%)	9 (7.1)	8 (6.6)	0.869
ICU admission, n (%)	3 (2.4)	1 (0.8)	0.643
Inpatient days (day), mean ± SD	4.6 ± 3.7	7.2 ± 7.2	0.000

APH, antepartum hemorrhage. ASA, the American Sociological Association. CD, cesarean delivery. EBL, estimated blood loss. PRBC, packed red blood cells. HGB, hemoglobin. HCT, hematocrit. PPH, postpartum hemorrhage. ICU, intensive care unit.

Neonatal outcomes were also significantly different between the 2 groups. The APH group manifested a higher rate of preterm delivery and a lower birth weight ($P < 0.001$) relative to the non-bleeding group. Infants with an Apgar score of less than 7 at 1 minute had a higher prevalence of APH compared to those without APH ($P = 0.003$), but there was no difference in infants with an Apgar score of less than 7 at 5 minutes ($P = 0.09$). The number of newborns admitted to the neonatal intensive care unit (NICU) was also statistically different between the 2 groups, while the women with APH exhibited a higher admission rate than those without APH ($P = 0.002$) (Table 3).

Table 3
Neonatal outcomes in parturients with placenta previa

	Without APH	With APH	
	(n = 126)	(n = 121)	P value
Gestational age (weeks), mean ± SD	37.1 ± 1.6	35.6 ± 1.9	0.000
Newborn birth weight (grams), mean ± SD	2920 ± 524	2686 ± 544	0.000
Apgar score at 1 min, n (%)			0.003
≤ 7	23 (18.3)	42 (34.7)	
> 7	103 (81.7)	79 (65.3)	
Apgar Score at 5 min, n (%)			0.090
≤ 7	7 (5.6)	14 (11.6)	
> 7	119 (94.4)	107 (88.4)	
Preterm delivery, n (%)	41 (32.5)	90 (74.4)	0.000
Endotracheal intubation of newborns, n (%)	40 (31.7)	52 (43.3)	0.060
NICU admission, n (%)	47(37.3)	68 (56.7)	0.002
APH, antepartum hemorrhage. NICU, neonatal intensive care unit.			

Discussion:

In our investigation, we observed that the prevalence of APH in patients with placenta previa was 49%, which is consistent with reports of 32.0–77.1% in other countries[2, 3, 9–12], and similar to the 51.9% reported in a systematic review of studies worldwide.[13]

We found that the number of APH events varied between 1 and 7 episodes, with nearly half of the patients experiencing 2–3 incidents throughout their pregnancies. The incidence of APH was distinct for each gestational week, with the 32nd gestational week appearing to be the most precarious and possessing the highest incidence of APH. We evaluated the incidence of APH in placenta previa patients as it was first described and during the gestational week in which it occurred, and to the best of our knowledge, there are no other extant reports on this specific topic. In general, the 32nd week marked a turning point in that prior to 32 weeks, bleeding gradually increased commensurate with increasing gestational week. However, after 32 weeks, the bleeding began to diminish. This pattern appears to be consistent with data demonstrating that as the numbers of CDs gradually increase commensurately with the increase in gestational weeks, the resulting incidence of vaginal bleeding is markedly reduced.[14] It is possible that augmented uterine contractions (particularly after 32 weeks) may lead to a shortened

cervical length and further separation of the placenta from the uterine wall, thus allowing hemorrhaging to occur more readily. Previous investigators have postulated that the etiology of APH in placenta previa is a poor blood supply that induces atrophy of thin portions of the placenta implanted over the cervix; this subsequently leads to placental migration as gestation continues, ensuring an improved blood supply from a more richly vascularized area (a process known as trophotropism).[15] Oppenheimer et al. [16] reported that the placenta did not overlap the internal os consistently; rather, placental migration occurred at an average rate of + 5.4 mm/week, while the rate was only + 0.3 mm/week in placenta previa.[16] Uterine contractions, cervical effacement, and dilatation during the third trimester can also cause separation of the placenta, which leads to small amounts of bleeding; this bleeding may subsequently stimulate further placental separation and unavoidable hemorrhage.[17]

Our finding of complete placenta previa as a risk factor for APH is consistent with prior studies. Bahar et al., for example, reported that women with major (complete or partial) placenta previa manifested a significantly higher incidence of APH (OR, 3.18; 95% CI, 1.58–6.4; P = 0.001).[3] Similarly, Atsuko et al. reported that APH was more prevalent in women with complete placenta previa compared to those with incomplete previa (59.1% vs. 17.6%: OR, 6.79; 95% CI, 3.31–13.92).[18] Yang et al. also reported a higher frequency of APH in complete previa compared to marginal previa.[19] From these studies, it appears that complete previa is likely to be an independent risk factor in predicting APH in these patients. Some authors have also used ultrasonography to identify short uterine cervical length (observed in the third trimester) and the sinus venosus at the margin of the placenta as risk factors for APH in placenta previa.[20] Stafford et al. demonstrated that in the third trimester, a cervical length of 30 mm or less was associated with an increased risk for hemorrhage (79% vs 28%) in placenta previa patients,[21] whereas Saitoh et al. reported that the risk of massive antenatal hemorrhage was higher (83.3%) in placenta previa patients with an echo-free space in the placental edge overlying the internal os compared to other locations (7.7–10%).[22] We must, however, admit that the evidence remains controversial, with other investigators showing contrasting results. Hasegawa et al. maintained that the use of ultrasonography could not predict bleeding episodes,[10] and according to the 2011 RCOG guidelines, APH possesses a heterogeneous pathophysiology and thereby cannot be predicted reliably.[7] Intriguingly, the location of the placenta was not reported to influence APH,[18] and the anterior placenta may only increase hemorrhage during and after CD.[23] Contradicting our original hypothesis, placenta accreta did not serve as a protective factor in ameliorating APH.

With regard to maternal outcomes, we also demonstrated that recurrent or major APH enhanced hospitalizations, led to maternal anemia, and increased emergent CDs, blood transfusion rate, and total blood-product infusion; these findings were also confirmed by Takayama[24] and Crane et al.[25] Although these authors also reported that APH elevated rates of hysterectomy[24] and PPH,[25, 26] we did not find an increase in bleeding with hysterectomy or PPH in our study. We additionally treated our hysterectomy or PPH patients with various hemostatic methods including uterine balloons, B-Lynch sutures, arterial ligation, or bilateral uterine artery embolization. We also found that patients with APH were more likely to

have undergone general anesthesia, which was probably due to their greater chance of requiring emergent delivery. Since general anesthesia (GA) is associated with a higher risk for PPH in CD[27–29], routine CDs are commonly performed using neuraxial anesthesia following guidelines that also recommend using neuraxial anesthesia in placenta previa.[1] In the present study, 4.0% of all patients underwent GA (consistent with a previous report by Markley et al. [5%]),[30] and of the patients who underwent GA, 70% underwent emergent CS for APH. It is possible that the massive bleeding associated with APH led to unstable maternal hemodynamics or intrauterine fetal hypoxia, which would not have allowed enough time to prepare for the use of neuraxial techniques. At our institution, electively scheduled CDs for placenta previa are performed at 36–37 weeks of gestation, and preterm CD is performed only when massive, uncontrollable hemorrhage or fetal distress occurs. The American Society for Maternal-Fetal Medicine (SMFM) and the RCOG guidelines both recommend delivery dates for placenta previa to be between 36^{+0} and 37^{+0} weeks of gestation for women who are stable and show no bleeding.[1, 31] In placenta previa patients with a history of vaginal bleeding or other associated risk factors, delivery should be considered between 34^{+0} and 36^{+6} weeks of gestation.[1] SMFM also recommends that for women with active hemorrhaging in the late preterm period, delivery should not be delayed for the purpose of administering antenatal corticosteroids. [31]

Many studies have shown that recurrent APH causes higher rates of NICU admission, preterm delivery,[32] stillbirth, death,[33] and other adverse neonatal outcomes[34],which is consistent with our current results. These adverse outcomes may be due to recurrent antenatal vaginal bleeding that affects the placental blood supply, which subsequently leads to insufficient fetal blood supply.[5] In contrast, however, some investigators have not found that severe bleeding leads to increased adverse maternal or neonatal outcomes.[35] The discrepancies among these aforementioned studies may reflect differences in maternal background and patient management, and suggest that additional large, multicenter studies are needed to confirm the effects of APH on both maternal and neonatal outcomes.

To our knowledge, this is the first study to identify an association between APH in placenta previa patients and gestational week. Our work adds to the important literature regarding risk factors for APH and its significant implications for maternal and neonatal outcomes. Although it is difficult to reliably predict APH among women, we identified the third trimester—especially around 32 weeks—as a potential turning point with respect to bleeding risk. We also found complete placenta previa to be an independent risk factor for APH in this specific patient population.

Several limitations to this study should be noted. First, this was a relatively small study limited to one healthcare system, which may result in informational and regional biases that require increased case numbers and an expanded research area. Second, because of the retrospective nature of the study design, we were unable to collect and report on data regarding other important information, including the amount of APH, cervical length, umbilical arterial blood gas values, and long-term neonatal complications. In the future, large prospective studies are needed to assist clinicians and researchers in better understanding the risks and implications of APH in placenta previa patients.

Conclusions:

The gestational week and frequency of APH varied by patient with placenta previa and might have resulted in an increase in adverse maternal and neonatal outcomes. Clinicians should thus be cognizant of placenta previa as increasing the risk for prenatal bleeding, especially in the third trimester at approximately the 32nd gestational week. It is also important for clinicians to recognize that women who do experience APH may be at higher risk for requiring blood transfusions and undergoing emergent CD, and their newborns are at an increased likelihood for manifesting lower birth weight, asphyxia, and additional NICU admissions. Pediatric involvement in the delivery of these patients may therefore be warranted. Thus, healthcare providers should consider transferring patients with complete placenta previa to a tertiary medical center to tailor their personal antenatal management, identify potential risks and outcomes, and provide advanced, multidisciplinary care to prevent adverse consequences.

Abbreviations

CD: Cesarean delivery; APH:Antepartum hemorrhage; PHS:Partners Healthcare System; EMR:Electronic medical records; BMI:Body mass index; IVF:In vitro fertilization; PRBC:Packed red blood cells; FFP:Fresh frozen plasma; PPH:Postpartum hemorrhage; EBL:Estimated blood loss; HGB:Hemoglobin; HCT:Hematocrit; SPSS:Statistical Package for the Social Sciences; SD:Standard deviation; OR:Odds ratio; CI:Confidence interval; GA:General anesthesia; SMFM:Society for Maternal-Fetal Medicine

Declarations

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

Wenjie Qing drafted the manuscript and participated in data collection and analysis; Linda Li analyzed data and prepared the manuscript; Alyssia Venna performed the statistical analysis and reviewed the manuscript; and Jie Zhou contributed to the development of the study, the study design, and manuscript preparation for publication.

All authors read and approved the final manuscript.

Ethics approval and consent to participate

The authors confirm that they obtained approval by the Ethics Committee of Brigham and Women's Hospital, Harvard Medical School; and that written consent for use of the data in scientific research was also acquired from patients before operation.

Consent for publication

Not applicable.

Competing interests

All the authors declare that they have no competing interests.

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Figures

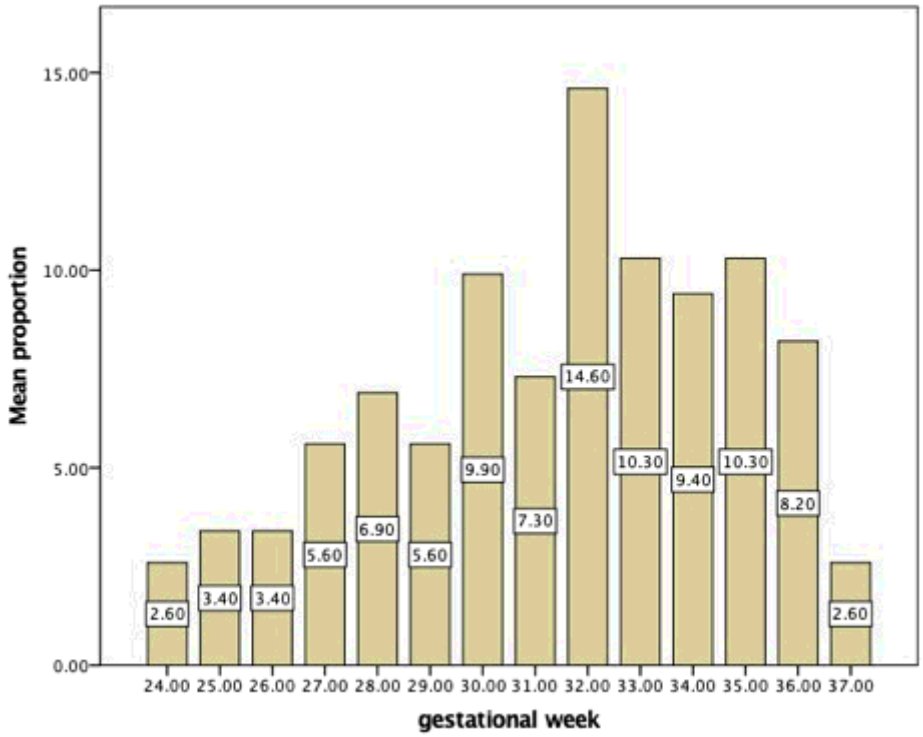

Figure 1

Figure 1

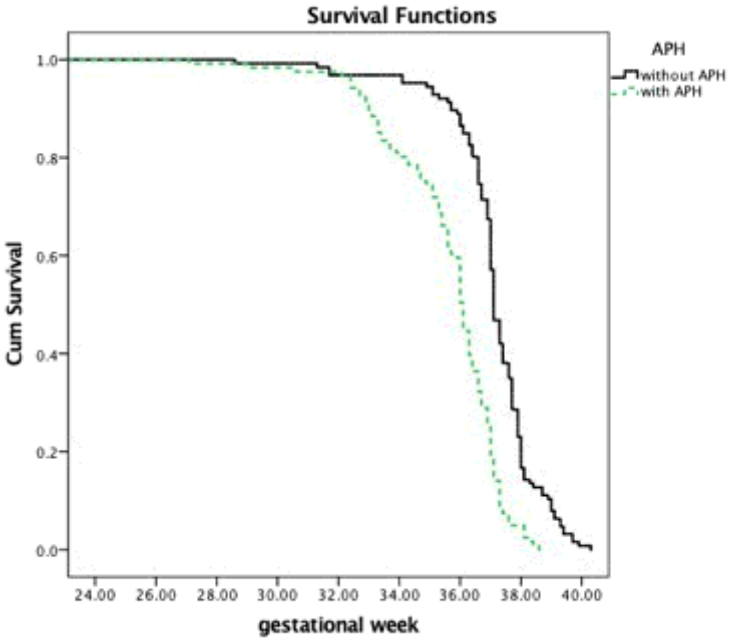

Figure 2

Figure 2