UNIVERSITÉ TOULOUSE III – PAUL SABATIER
FACULTÉS DE MÉDECINE

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THÈSE

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C'est un honneur de t'avoir en tant que président de mon jury de thèse.
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Sois assuré de mon plus profond respect.

Monsieur le Docteur Paul GUERBY
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Sois assuré de ma plus grande gratitude.

Madame le Docteur Béatrice GUYARD-BOILEAU
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Praticien Hospitalier
Gynécologue-Obstétricien

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Table des matières

Abbreviations

AHUO: Antepartum hemorrhage of unknown origin

APH: Antepartum hemorrhage

HAS : Haute Autorité de Santé

IQR : Interquartile ranges

IUGR: Intrauterine growth restriction

NICU : Neonatal intensive care unit

PDV : Paule de Viguier maternity

PMSI : Programme de médicalisation du système d'information

PE: Preeclampsia

PP: Placenta previa

PROM: Premature rupture of membranes

RCOG: Royal College of obstetricians and gynaecologists

ROC: receiver operator characteristic

SMFM: Society for Maternal-Fetal Medicine

SOGC: Society of Obstetricians and Gynecologists of Canada

TPD: Threatened preterm delivery

WG: Weeks of gestation

Introduction

Epidemiology and definitions

Third trimester bleeding, or antepartum hemorrhage (APH), is defined as bleeding from the genital tract during the second half of pregnancy (between 24 weeks of gestation and birth). Although they remain an uncommon event, they complicate 3-5% of pregnancies and represent an important cause of perinatal mortality and maternal morbidity worldwide.(1)(2) Besides unknown origin, the main causes of APH are placenta previa (PP) and placental abruption (retroplacental or marginal). Other causes may be related to cervical or vaginal lesions, bloody show associated with labor or premature rupture of membranes (PROM), or less commonly, uterine rupture, Benckiser's hemorrhage (vasa previa).(3)
The most serious etiologies requiring emergency fetal extraction by cesarean section, namely, placental abruption, Benckiser's hemorrhage, or uterine rupture, should be systematically sought in the first instance.

Despite their great clinical importance, placenta previa and placental abruption account for only a minority of cases of antepartum hemorrhage, the majority being of unknown origin. Antepartum hemorrhage of unknown origin (AHUO) or unexplained APH is a diagnosis of exclusion but could account for nearly 40% of APH. (4)
Pregnancies complicated by AHUO are also at increased risk of adverse maternal and perinatal outcomes, such as preterm delivery, reduced birth weight, and therefore stillbirth. (5)(6)(7)(8)(9)
In particular, Watad et al. reported in a retrospective cohort of 230 women presenting AHUO between 2003 and 2014, compared to 51 468 control pregnant women, that a single episode of vaginal bleeding of unknown etiology between 24 weeks and 34 weeks appears to be an independent risk factor for preterm delivery. (10)

Placenta previa refers to the presence of placental tissue that extends over the internal cervical os and is associated with maternal and neonatal adverse outcomes, as well as the potential for severe APH and postpartum hemorrhage. (11)
The overall prevalence of APH in pregnant women with placenta previa was 51.6% according to the meta-analysis by Fan et al. (12)

Numerous studies have shown that the presence of APH in placenta previa is associated with a significantly increased risk of preterm delivery and reduced birth weight compared with patients with placenta previa who do not have antepartum hemorrhage. (13)(14)(15)
According to the Society of Obstetricians and Gynecologists of Canada (SOGC), a history of APH (first episode before 29 weeks or recurrent episodes [≥3]), a placental edge covering the cervical os, short cervical length (less than 3 cm in placenta previa, less than 2 cm in low inserted placenta) are risk factors associated with an increased risk of preterm delivery or emergency cesarean section. (16)

Marginal or subchorionic abruption corresponds to a marginal abruption of the placenta, which is also associated with an increased risk of preterm delivery. (17)(18)(19)

Hospitalizations for APH after 24 weeks of gestation thus represent a significant proportion of hospitalizations of pregnant women.

International guidelines

There are few or no precise recommendations on the optimal indications and duration of hospitalization according to the etiology of APH.
According to the Royal College of obstetricians and gynaecologists (RCOG) :

- For symptomatic placenta previa, antenatal care including the necessity and the duration of hospitalization should be tailored on a case-by-case basis (depending on geographic location, social circumstances, and number of previous episodes of bleeding) (20)
- For AHUO, women with spotting that no longer bleeds and in whom placenta previa has been excluded can be discharged home after a reassuring initial clinical assessment. In contrast, patients with bleeding greater than spotting should remain in hospital at least until the bleeding has stopped. (21)

According to the Society of Obstetricians and Gynaecologists of Canada (SOGC), bed rest or reduced activity is not beneficial for women with placenta previa and can be potentially associated with poorer outcomes. In women with placenta previa and in the presence of risk

factors (bleeding episodes, history of preterm delivery), hospital management should be considered. (16)

The Cochrane systematic review, which has not been updated since October 2002 and includes only one small randomized clinical trial (n=53), compared hospital and home care for symptomatic placenta previa. This trial found little evidence in favor of a policy of home care over hospital care, other than reduced length of hospital stay. (22)

The protocol in our maternity hospital is as follows:

- In case of APH associated with placenta previa: hospitalization for a minimum of 7 days, with a discharge envisaged after cessation of bleeding if the first or second episode of bleeding. After the third episode, a definitive readmission of the patient is carried out.
- In case of AHUO or marginal abruption: hospitalization for a minimum of 48 hours with a discharge envisaged 48 hours after cessation of bleeding.

Literature data

In the literature, the results are divergent.

O. Ogueh showed in a retrospective study of 219 women between 1993 and 1995 that hospitalization for AHUO did not confer any benefit in terms of gestation at delivery, birth weight, Apgar score, and recurrence of bleeding, and that length of stay was not significantly related to gestational age at delivery or to birth weight or Apgar score. (23)

In G. Roberts study performed in 1970, perinatal mortality in cases of AHUO was higher than in cases of placenta previa (27.2% vs. 7.6% for placenta previa). The authors reported that preterm labor started within 7 days of bleeding in the majority of AHUO that resulted in perinatal death. This study therefore suggests that in patients with AHUO, premature hospital discharge should not be considered simply because the placenta is in a normal position. (24)

In M. Heaman's study that includes a sample of 24 women who were interwiewed in 1994, it was shown that hospitalization was a source of stress for patients, and that it might be interesting to propose and develop home care programs as an alternative to hospitalization for APH.(25)

Finally, according to the Society for Maternal-Fetal Medicine (SMFM), many reports have shown that activity restriction, and in particular prolonged hospitalization, does not prevent

adverse obstetrical outcomes, but leads to significant physical (especially thromboembolic risks) and psychosocial risks. (26)

Therefore, there are no clear data in the literature on the prognosis, benefit and duration of hospitalization for APH.

Study objective

The main objective of our study is to evaluate the factors associated with a delivery within 7 days in case of APH between 24 and 37 weeks of gestation, according to the etiology. Secondly, we will analyze perinatal outcomes according to the etiology of APH.

Materials et methods

Study design

This is a retrospective cohort study conducted in the Paule de Viguier maternity hospital of Toulouse from January 1, 2015, to December 31, 2019. This is a type 3 maternity hospital performing more than 5000 deliveries per year during the study period.

Maternal and fetal medical data were collected from paper obstetrical records, partially computerized (Orbis software), in compliance with the laws on "informatique et libertés".

Study population

All hospitalizations for APH after 24 WG and before 37 WG were extracted from the “programme de médicalisation du système d’information” (PMSI) data and classified into 3 groups: APH related to placenta previa, APH related to a marginal abruption, and unexplained APH (AUHO).

We included all women hospitalized for a first episode of APH, not requiring immediate emergency delivery, between 24 WG and 37 WG.

We chose the threshold of 24 weeks of gestation, since this is the threshold from which fetal management can be considered in our maternity hospital, with the possibility of carrying out

antenatal corticosteroid therapy for fetal lung maturation. And after 37 weeks of gestation because we were interested in women for whom an expectant attitude could be proposed.
The criteria for non-inclusion were: any episode of APH occurring before 24 weeks or after 37 weeks, any episode of severe initial APH requiring emergency delivery even before hospitalization for monitoring (placental abruption, severe bleeding, uterine rupture…), and multiple pregnancies.
We excluded any episode of APH related to another cause than the three studied: cervical or vaginal lesions, bloody show associated with labor or premature rupture of membranes (PROM).

Study aims

The primary outcome was defined as any delivery occurring within 7 days of hospitalization.
Secondary outcomes were defined as deliveries within 48 hours of hospitalization. They also included neonatal outcomes (preterm birth, birth weight, umbilical cord pH, Apgar, etc) and maternal outcomes (postpartum hemorrhage, complications, death, etc).

Statistical analysis

All data were analyzed using Stata 16.1 (StataCorp, College Station, TX) statistical software.
Patient characteristics are described as proportions for categorical variables and as medians and interquartile ranges (IQR) for quantitative variables.
The distributions in the groups were compared and evaluated by Fischer's Exact Test for the qualitative variables, and by Student's T-test for the quantitative variables. Variables were compared according to the etiology of the bleeding.
For secondary analysis (maternal and neonatal outcomes at birth) we excluded patients who had given birth in another maternity hospital or who had been transferred before delivery to another maternity hospital.
We performed a subgroup analysis of women presenting APH before 34 weeks of gestation, in order to study this population for which we discuss lung maturation.
These variables were analyzed in univariate analysis according to the outcomes "delivery within 7 days", "delivery within 48 hours", "delivery before 37 weeks" and "delivery before 34 weeks".

Characteristics that showed a statistically significant association and chronological plausibility with the studied outcome were included in a multivariate logistic regression analysis. The predictive ability of these regression models is presented through receiver operator characteristic (ROC) curves, whose area under the curve was calculated.

For the survival analysis, delivery was considered the study event. If the exact time of delivery was unknown, the participant was still included and her survival time censored until discharge (loss of sight). Analysis was obtained using Cox proportional hazards model regression. Survival curves were plotted according to Kaplan-Meier methodology.

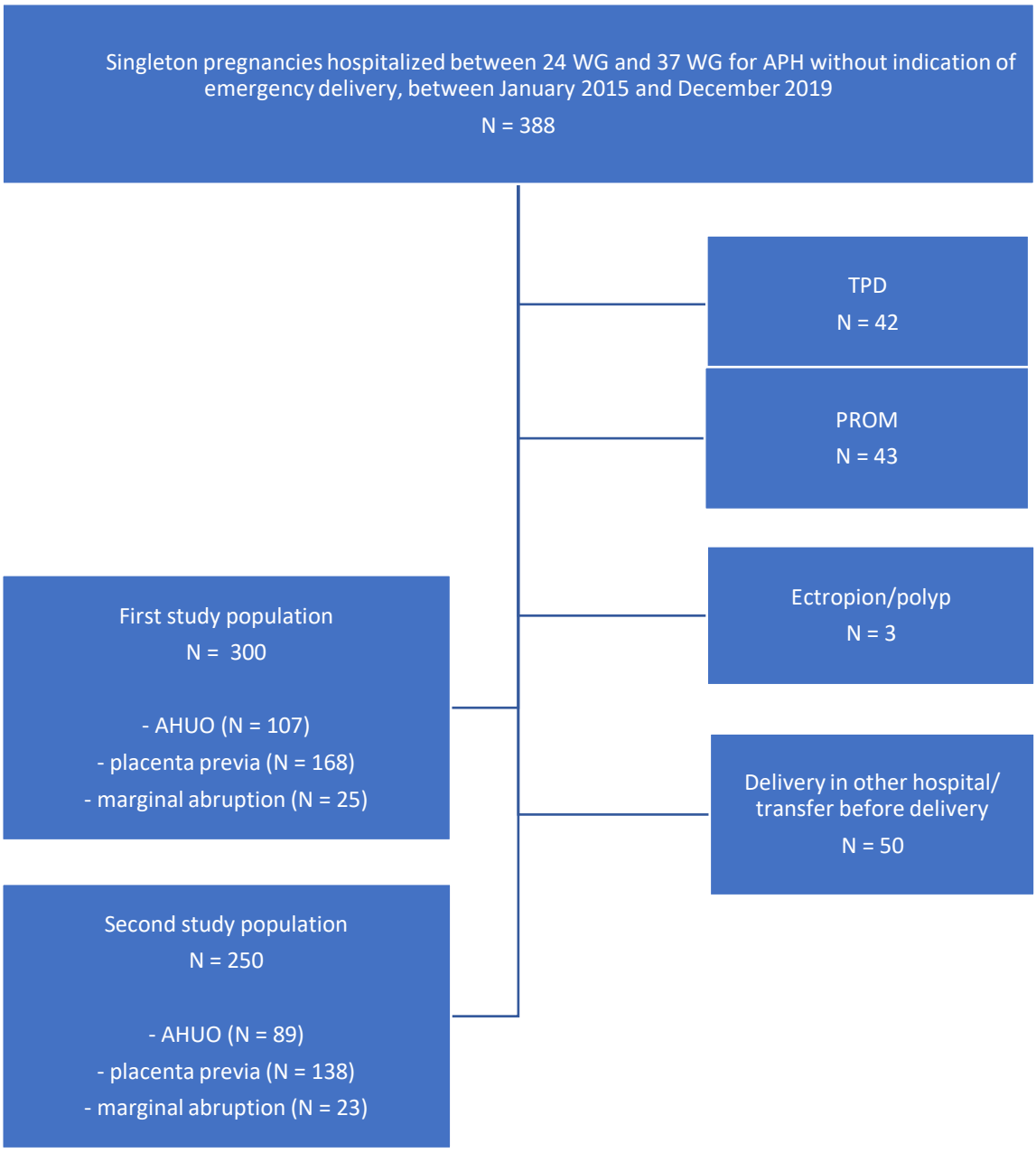
A p value less than 0.05 indicated statistical significance.

Ethics

No external funding was received for this study.

Our study obtained the approval MR-004 from the research and innovation department of Toulouse University Hospital.

Figure 1. Flow chart



AHUO: Antepartum hemorrhage of unknow origin
WG: weeks of gestation
TPD: Threatened preterm delivery
PROM: Premature rupture of membranes

Results

Between January 1, 2015, and December 31, 2019, we included 388 women hospitalized for a first episode of APH between 24 weeks and 36 weeks and 6 days. We excluded 42 women whose APH origin was related to threatened preterm delivery, 43 women related to premature rupture of membranes, 3 women related to cervical or vaginal lesions (ectropion and endocervical polyp).

For the analysis of the outcomes "delivery within 7 days" and "delivery within 48 hours" our first study population included 300 women, of which 107 women hospitalized for AHUO, 168 related to placenta previa, and 25 related to a marginal abruption.

For the analysis of secondary outcomes, we excluded 50 women who delivered in another maternity hospital or were transferred before delivery to another maternity hospital, so our second study population included 250 women, 89 of whom were hospitalized for AHUO, 138 for placenta previa, and 23 for marginal abruption. (Figure 1)

The characteristics of the population are described in Table 1 and Table 2. We can observe that maternal and fetal morbidity is increased in the 3 groups. This is particularly observed in the placenta previa and marginal abruption groups, with a higher rate of preterm birth (gestational age at delivery respectively 36 WG and 4 days and 33 WG and 4 days) associated with a reduction of birth weight (respectively 2680 g and 2140 g). There was also a higher rate of postpartum hemorrhage in the placenta previa group, with a higher rate of transfusion (16.7% $p < 0,001$).

In univariate analysis:

- Delivery within 7 days (Table 3): the etiology placenta previa is not associated with a risk of delivery within 7 days (OR 0.45 (0.20 - 0.98) p = 0.046). In contrast, the presence of APH related to a marginal abruption is significantly associated with a risk of delivery within 7 days (OR 3.35 (1.20-9.32) p = 0.028). In the subgroup “APH before 34 weeks” (table 5), the etiology placenta previa is not associated with a risk of delivery within 7 days (OR 0.22 (0.07 - 0.67) p = 0.008), in contrast to the etiology marginal abruption which is significantly associated with a risk of delivery within 7 days (OR 3.92 (1.10 – 13,95) p = 0.048).

- Delivery within 48 hours (Table 4): The presence of APH related to a marginal abruption appears to be significantly associated with a risk of delivery within 48 hours (OR 4.43 (1.10 – 17.91) p = 0.057). In the subgroup “APH before 34 weeks” (table 6), the etiology marginal abruption is significantly associated with an increased risk of delivery within 48 hours (OR 10.22 (1,36 – 76,97) p = 0.048).
- Delivery before 37 weeks of gestation (Table 7): The presence of AHUO was not statistically associated with a risk of delivery before 37 weeks (OR (0.10-0.33) p < 0.001). On the other hand, the presence of APH related to placenta previa or marginal abruption would seem to be significantly associated with a risk of delivery before 37 weeks (OR 2.94 (1.73-5.01) p < 0.001 and OR 3.29 (1.30-8.32) p = 0.014, respectively). Stratifying on the cause of bleeding (Table 11), we note that the duration of hospitalization during the first episode of APH is not significantly associated with a risk of delivery before 37 weeks, whatever the cause. In the subgroup “APH before 34 weeks” (table 9), we observe the same trends.
- Delivery before 34 weeks (Table 8): The presence of AHUO is not associated with a risk of delivery before 34 weeks significantly (OR 0.38 (0.18 - 0.81) p = 0.013) and, on the other hand, the presence of APH related to a marginal abruption is statistically associated with a risk of delivery before 34 weeks (OR 5.78 (2.37 - 14.08) p < 0.001). Stratifying on the cause of bleeding (Table 12), we note that the duration of hospitalization during the first episode of bleeding is not significantly associated with a risk of delivery before 34 weeks, whatever the cause. In the subgroup “APH before 34 weeks” (table 10), we observe the same trends.

In multivariate analysis, the prediction models constructed would show that:

- Delivery within 7 days (Figure 2): the presence of IUGR, advanced gestational age, and quantity of bleeding at the first episode, would appear to be independent risk factors for delivery within 7 days of hospitalization, with an area under the curve (AUC) of 0.77 (95% CI 0.68 - 0.86) of the predictive model using these variables. In the subgroup of women presenting an APH before 34 weeks (figure 5), APH related to placenta previa is associated with a lower risk of delivery within 7 days, and in the other hand, the presence of IUGR, the abundance of bleeding and the gestational age at the first episode are associated with a higher risk, with an AUC of 0.84 (CI 95% 0.72 - 0.92).

- Delivery within 48 hours (Figure 3): The presence of AHUO is a factor independently associated with a decreased risk of delivery within 48 hours, and advanced gestational age at first episode independently increases this risk, with an AUC of 0.83 (95% CI 0.73 - 0.94) of the model using. In the subgroup of women presenting an APH before 34 weeks (figure 6), APH related to marginal abruption and the presence of IUGR are independently associated with an increased risk of delivery within 48 hours, with AUC of 0,81 (CI 95% 0,56 – 1.00)
- Delivery before 37 weeks (Figure 7): the quantity of bleeding on admission, the number of recurrences after the first episode, the duration of the first episode, and the presence of IUGR are independent risk factors for delivery before 37 weeks, with an area under the curve (AUC) of 0.80 (95% CI 0.74 - 0.85). The presence of AHUO would be a predictive factor that would decrease the risk of delivery before 37 weeks. In the subgroup “APH before 34 weeks” (figure 9), we can observe the same trends, with an AUC of 0,81 (CI 95% 0,75 – 0,88).
- Delivery before 34 weeks (Figure 8): the abundance of bleeding on arrival, the duration of the first episode of bleeding, and the presence of intrauterine growth retardation are independent risk factors for preterm delivery before 34 weeks, with an AUC of 0.78 (95% CI 0.70-0.85). In the subgroup “APH before 34 weeks” (figure 10), APH related to marginal abruption, the duration of the first episode of bleeding and history of preterm delivery would appear to be independent risk factors for delivery before 34 weeks, with an AUC of 0.73 (CI 95% 0,65 – 0,82).

In the survival analysis (Figure 4), considering the different confounding factors (such as gestational age of the first episode, duration of bleeding, number of recurrences, history of preterm delivery, presence of IUGR) according to the cause of the bleeding, APH related to placenta previa or marginal abruption seem to be associated with a higher risk of preterm birth than AHUO. In the subgroup of women presenting an APH before 34 weeks (figure 11), we observe the same trends.

Table 1. Basal characteristics of the population according to the origin of bleeding
N=300

	CAUSE OF THE BLEEDING			
	PLACENTA PREVIA	MARGINAL ABRUPTION	AHUO	P-VALUE
	N = 168	N = 25	N = 107	
MATERNAL AGE (YEARS) [median (IQR)]	33.0 (7.0)	31.0 (7.0)	30.0 (9.0)	**0.000**
BODY MASS INDEX (KG/M2) [median (IQR)]	23.4 (6.5)	21.1 (3.7)	22.2 (5.6)	**0.005**
NUMBER OF PREVIOUS DELIVERIES [median (IQR)]	1.0 (2.0)	1.0 (1.0)	1.0 (1.0)	0.444
UTERINE SCARS [n (%)]	29 (17,2%)	4 (16%)	15 (14%)	0.356
SMOKING STATUS [n (%)]	30 (17.9%)	5 (20.0%)	23 (21.5%)	0.752
CHRONIC HYPERTENSION [n (%)]	2 (1.2%)	0 (0.0%)	3 (2.8%)	0.600
PREEXISTING DIABETES [n (%)]	3 (1.8%)	0 (0.0%)	2 (1.9%)	1.000
AUTOIMMUNE DISEASE BEFORE PREGNANCY [n (%)]	6 (3.6%)	0 (0.0%)	1 (0.9%)	0.389
ANTICOAGULANT TREATMENT [n (%)]	16 (9.5%)	0 (0.0%)	6 (5.6%)	0.203
GESTATIONAL DIABETES [n (%)]	39 (23.2%)	3 (12.0%)	18 (16.8%)	0.295
INTRAUTERINE GROWTH RESTRICTION [n (%)]	7 (4.2%)	1 (4.0%)	5 (4.7%)	1.000
PREECLAMPSIA [n (%)]	5 (3.0%)	0 (0.0%)	3 (2.8%)	1.000
GESTATIONAL AGE OF FIRST EPISODE OF BLEEDING (WEEKS) [median (IQR)]	30.8 (4.6)	30.4 (5.3)	33.1 (4.7)	**0.000**
DURATION OF THE FIRST EPISODE (DAYS) [median (IQR)]	1.0 (0.0)	1.0 (1.0)	1.0 (0.0)	**0.009**
DURATION OF THE HOSPITALIZATION (DAYS) [median (IQR)]	7.0 (4.0)	5.0 (5.0)	2.0 (1.0)	**0.000**
NUMBER OF RECURRENCES AFTER THE FIRST EPISODE [median (IQR)]	0.0 (1.0)	0.0 (1.0)	0.0 (0.0)	**0.000**
SPONTANEOUS BLEEDING [n (%)]	162 (96.4%)	24 (96.0%)	96 (89.7%)	0.072
SPOTTING [n (%)]	65 (38.7%)	6 (24.0%)	65 (60.7%)	**0.000**
MINOR BLEEDING [n (%)]	73 (43.5%)	11 (44.0%)	36 (33.6%)	0.264
MAJOR BLEEDING [n (%)]	30 (17.9%)	8 (32.0%)	6 (5.6%)	**0.000**
PRESENCE OF VASA PREVIA [n (%)]	10 (6.0%)	0 (0.0%)	0 (0.0%)	**0.015**
CERVICAL LENGTH (MM) [median (IQR)]	35.0 (12.0)	31.0 (14.5)	35.0 (10.0)	0.418
ANTENATAL CORTICOSTEROIDS [n (%)]	126 (75.0%)	21 (84.0%)	38 (35.5%)	**0.000**
GESTATIONAL AGE AT FIRST DOSE OF CORTICOSTEROIDS (WG) [median (IQR)]	29.9 (3.1)	29.0 (5.1)	30.8 (2.1)	**0.021**
DELIVERY WITHIN 7 DAYS OF HOSPITALIZATION [n (%)]	12 (7.9%)	6 (26.1%)	11 (12.2%)	**0.034**
missing values [n (%)]	*17 (10.1%)*	*2 (8.0%)*	*17 (15.9%)*	
DELIVERY WITHIN 48 HOURS OF HOSPITALIZATION [n (%)]	6 (3.6%)	3 (12.0%)	2 (2.0%)	0.084
DELIVERY BEFORE 34WG [n (%)]	27 (19.3%)	12 (52.2%)	10 (10.8%)	**0.000**
missing values [n (%)]	*28 (16.7%)*	*2 (8.0%)*	*14 (13.1%)*	
DELIVERY BEFORE TERM (< 37WG) [n (%)]	76 (55.1%)	16 (69.6%)	17 (19.1%)	**0.000**
missing values [n (%)]	*30 (17.9%)*	*2 (8.0%)*	*18 (16.8%)*	

Data are presented as n (%) or median (IQR) IQR: interquartile range, WG: weeks of gestation

Table 2. Basal characteristics of the population according to the origin of bleeding (women delivering at PDV)

N =250

	CAUSE OF THE BLEEDING			
	PLACENTA PRAEVIA N = 138	MARGINAL ABRUPTION N = 23	AHUO N = 89	P-VALUE
GESTATIONAL AGE AT DELIVERY (WEEKS) [median (IQR)]	36.6 (2.9)	33.6 (7.1)	39.0 (2.0)	**0.000**
TYPE OF DELIVERY				
SPONTANEOUS [n (%)]	20 (14.5%)	12 (52.2%)	58 (65.2%)	
INSTRUMENTAL DELIVERY [n (%)]	3 (2.2%)	2 (8.7%)	5 (5.6%)	**0.000**
ELECTIVE CESAREAN [n (%)]	54 (39.1%)	1 (4.3%)	7 (7.9%)	
EMERGENT CESAREAN [n (%)]	61 (44.2%)	8 (34.8%)	19 (21.3%)	
EMERGENCY CESAREAN DELIVERY [n (%)]	100 (72.5%)	8 (34.8%)	11 (12.4%)	**0.000**
INDUCTION OF LABOR [n (%)]	12 (8.7%)	3 (13.0%)	20 (22.5%)	**0.012**
EPIDURAL ANESTHESIA [n (%)]	33 (23.9%)	15 (65.2%)	71 (79.8%)	**0.000**
GENERAL ANESTHESIA FOR DELIVERY [n (%)]	12 (8.7%)	2 (8.7%)	1 (1.1%)	**0.028**
POSTPARTUM HEMORRHAGE [n (%)]	79 (57.2%)	7 (30.4%)	17 (19.1%)	**0.000**
IF POSTPARTUM HEMORRHAGE, QUANTITY (ML) [median (IQR)]	950 (900)	650 (300)	700 (350)	**0.048**
NEED OF TRANSFUSION [n (%)]	23 (16.7%)	0 (0.0%)	2 (2.2%)	**0.000**
MATERNAL DEATH [n (%)]	0 (0.0%)	0 (0.0%)	0 (0.0%)	N/A
LENGTH OF POST-PARTUM STAY (DAYS) [median (IQR)]	4.0 (1.0)	4.0 (2.0)	4.0 (1.0)	**0.005**
NEONATAL WEIGHT (G) [median (IQR)]	2680 (800)	2140 (1680)	3055 (720)	**0.000**
APGAR AT THE 5TH MINUTE [median (IQR)]	10.0 (0.0)	10.0 (0.0)	10.0 (0.0)	0.492
ARTERIAL PH (CORD BLOOD) [median (IQR)] *missing values [n (%)]*	7.3 (0.1) *16 (11.6%)*	7.2 (0.1) *2 (8.7%)*	7.2 (0.1) *14 (15.7%)*	**0.000**
ADMISSION TO NICU [n (%)]	10 (7.2%)	4 (17.4%)	1 (1.1%)	**0.007**
HOSPITALIZATION OF THE NEWBORN [n (%)]	50 (36.8%)	14 (60.9%)	10 (11.5%)	**0.000**
LENGTH OF TOTAL HOSPITALIZATION (DAYS) [median (IQR)]	5.0 (4.0)	9.0 (27.0)	4.0 (2.0)	**0.000**
NEONATAL DEATH [n (%)]	0 (0.0%)	0 (0.0%)	0 (0.0%)	N/A
DELIVERY WITHIN 7 DAYS OF HOSPITALIZATION [n (%)]	12 (8.7%)	6 (26.1%)	11 (12.4%)	0.054
DELIVERY WITHIN 48 HOURS OF HOSPITALIZATION [n (%)]	6 (4.3%)	3 (13.0%)	2 (2.2%)	0.070
DELIVERY BEFORE TERM (< 37W) [n (%)]	76 (55.1%)	16 (69.6%)	17 (19.1%)	**0.000**
DELIVERY BEFORE 34W [n (%)]	25 (18.1%)	12 (52.2%)	6 (6.7%)	**0.000**
ANTENATAL CORTICOSTEROIDS [n (%)]	98 (71.0%)	19 (82.6%)	27 (30.3%)	**0.000**
ADMINISTERED DOSES OF CORTICOSTEROIDS [median (IQR)]	2.0 (2.0)	2.0 (0.0)	0.0 (2.0)	**0.000**
GESTATIONAL AGE AT FIRST DOSE OF CORTICOSTEROIDS (W) [median (IQR)]	29.2 (3.4)	29.0 (5.6)	30.7 (3.0)	0.103
GESTATIONAL AGE AT SECOND DOSE OF CORTICOSTEROIDS (W) [median (IQR)]	29.4 (3.4)	28.6 (4.9)	30.9 (3.0)	0.078

Data are presented as n (%) or median (IQR) , NICU: Neonatal Intensive Care Unit

Table 3. Univariate analysis to delivery within 7 days of hospitalization (N = 300)

	Delivery within 7 days of hospitalization		OR (CI 95%)	p-value
	No N = 235	Yes N = 29		
AHUO [n (%)]	79 (33.6%)	11 (37.9%)	1.21 (0.54 - 2.68)	0.680
APH in placenta previa [n (%)]	144 (61.3%)	12 (41.4%)	**0.45 (0.20 - 0.98)**	**0.046**
APH in marginal abruption [n (%)]	17 (7.2%)	6 (20.7%)	**3.35 (1.20 - 9.32)**	**0.028**
Gestational age of first episode of bleeding (w) [median (IQR)]	31.3 (5.6)	33.9 (4.4)	**1.26 (1.09 - 1.45)**	**0.000**
Spotting [n (%)]	112 (47.7%)	9 (31.0%)	0.49 (0.22 - 1.13)	0.114
Minor bleeding [n (%)]	89 (37.9%)	12 (41.4%)	1.16 (0.53 - 2.54)	0.840
Major bleeding	34 (14.5%)	8 (27.6%)	2.25 (0.92 - 5.49)	0.101
Duration of the first episode (days) [median (IQR)]	1.0 (0.0)	1.0 (0.0)	1.05 (0.48 - 2.27)	0.681
Cervical length (mm) [median (IQR)]	35.0 (12.0)	35.0 (13.0)	0.99 (0.94 - 1.04)	0.734
Intrauterine growth restriction [n (%)]	9 (3.8%)	4 (13.8%)	**4.02 (1.15 - 14.00)**	**0.042**
Previous preterm delivery [median (IQR)]	0.0 (0.0)	0.0 (0.0)	2.24 (0.75 - 6.76)	0.090
Gestational age at delivery (weeks) [median (IQR)]	37.9 (3.1)	34.4 (4.1)	**0.72 (0.63 - 0.82)**	**0.000**

Data are presented as n (%) or median (IQR)

Table 4. Univariate analysis according to delivery within 48 hours of hospitalization (N= 293)

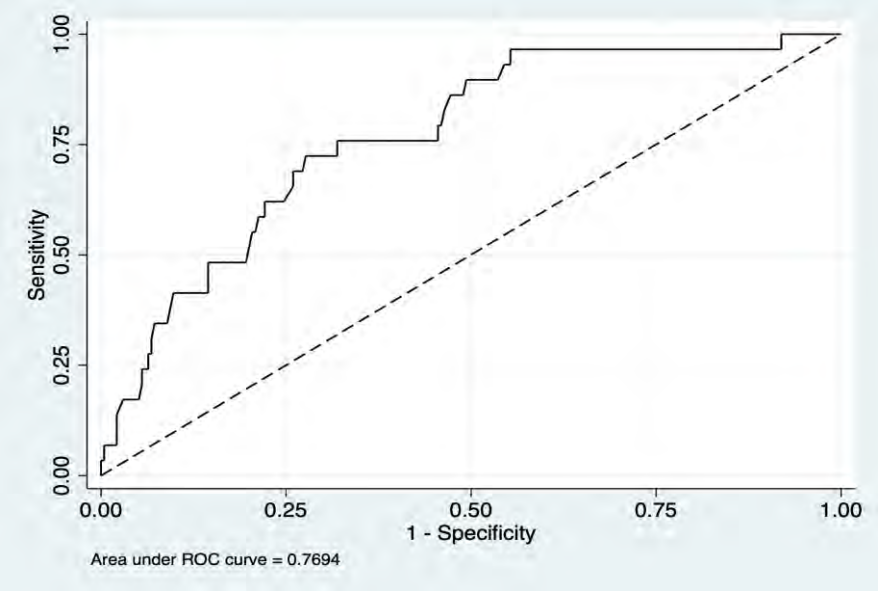
	Delivery within 48 hours of hospitalization		OR (CI 95%)	p-value
	No N = 282	Yes N = 11		
AHUO [n (%)]	98 (34.8%)	2 (18.2%)	0.42 (0.09 - 1.97)	0.342
APH in placenta previa [n (%)]	167 (59.2%)	6 (54.5%)	0.83 (0.25 - 2.77)	0.764
APH in marginal abruption [n (%)]	22 (7.8%)	3 (27.3%)	**4.43 (1.10 - 17.91)**	0.057
Gestational age of first episode of bleeding (w) [median (IQR)]	31.3 (5.4)	35.3 (3.1)	**1.52 (1.14 - 2.04)**	**0.001**
Spotting [n (%)]	128 (45.4%)	4 (36.4%)	0.69 (0.20 - 2.40)	0.759
Minor bleeding [n (%)]	114 (40.4%)	3 (27.3%)	0.55 (0.14 - 2.13)	0.535
Major bleeding [n (%)]	40 (14.2%)	4 (36.4%)	3.46 (0.97 - 12.35)	0.066
Duration of the first episode (days) [median (IQR)]	1.0 (0.0)	1.0 (0.0)	0.40 (0.05 - 3.00)	0.360
Cervical length (mm) [median (IQR)]	35.0 (10.0)	37.0 (14.0)	1.01 (0.93 - 1.09)	0.953
Intrauterine growth restriction [n (%)]	12 (4.3%)	1 (9.1%)	2.25 (0.27 - 19.04)	0.398
Previous preterm delivery [median (IQR)]	0.0 (0.0)	0.0 (0.0)	2.40 (0.61 - 9.45)	0.113
Gestational age at delivery (weeks) [median (IQR)]	37.7 (3.4)	35.3 (2.9)	**0.81 (0.68 - 0.96)**	**0.002**

Data are presented as n (%) or median (IQR)

Figure 2. Multivariate analysis according to delivery within 7 days of hospitalization (N = 264)

PREDICTIVE CAPACITY OF A MODEL INCLUDING THE ABOVEMENTIONED VARIABLES

AUC = 0.77 (CI 95% 0.68 - 0.86)

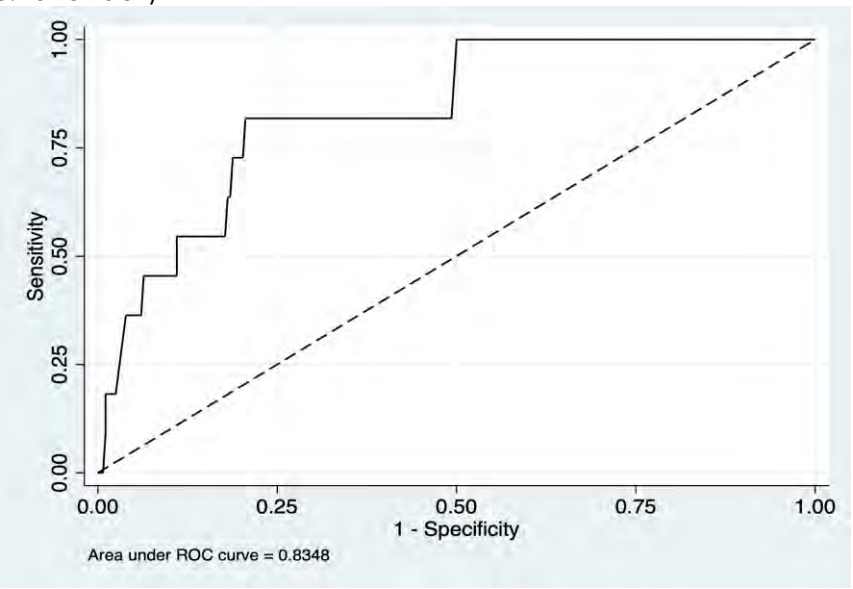


VARIABLE	OR (CI 95%)	P-VALUE
Gestational age of first episode of bleeding (days)	1.04 (1.02 - 1.07)	0.000
Intrauterine growth restriction	8.01 (2.02 - 31.77)	0.003
Quantity of bleeding	1.94 (1.13 - 3.33)	0.016

Figure 3. Multivariate analysis according to delivery within 48 hours of hospitalization (N = 293)

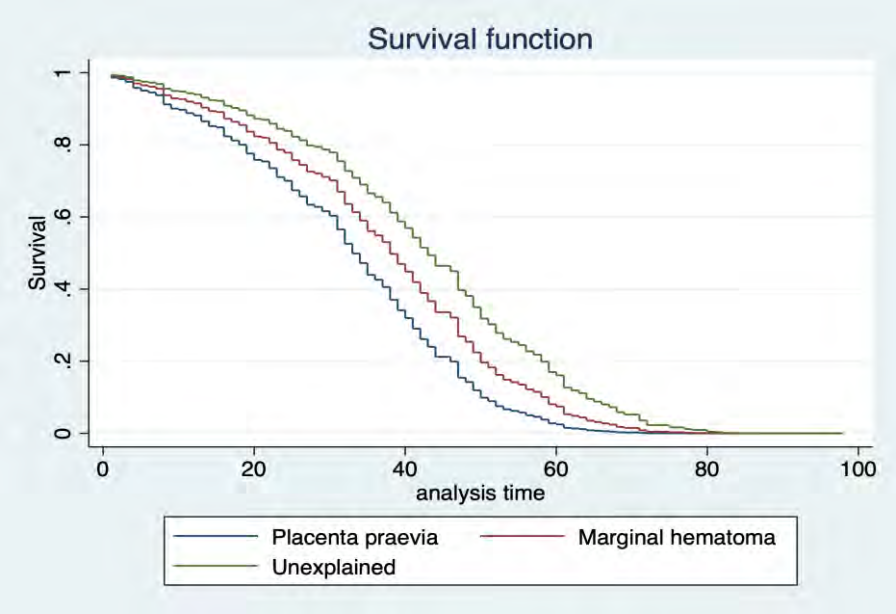
PREDICTIVE CAPACITY OF A MODEL INCLUDING THE ABOVEMENTIONED VARIABLES

AUC = 0.83 (CI 95% 0.73 - 0.94)



VARIABLE	OR (CI 95%)	P-VALUE
Gestational age of first episode of bleeding (days)	1.07 (1.03 - 1.12)	0.001
AHUO	0.19 (0.04 - 0.94)	0.042

Figure 4. Survival analysis: time from admission until delivery using cause bleeding



VARIABLE	HR (CI 95%)	P-VALUE
Gestational age of first episode of bleeding (days)	1.06 (1.05 - 1.07)	0.000
Cause of the bleeding	0.70 (0.61 - 0.82)	0.000
Intrauterine growth restriction	2.19 (1.23 - 3.89)	0.008
Number of recurrences after the first episode	1.12 (1.04 - 1.22)	0.004
Duration of the first episode (days)	1.61 (1.25 - 2.05)	0.000
Previous preterm delivery	2.35 (1.42 - 3.87)	0.001

Table 5. Univariate analysis to delivery within 7 days of hospitalization in subgroup "APH before 34 WG". (N = 211)

	Delivery within 7 days of hospitalization		OR (CI 95%)	p-value
	No	Yes		
	N = 165	N = 15		
AHUO [n (%)]	41 (24.8%)	6 (40.0%)	2.02 (0.68 - 6.01)	0.224
APH in placenta previa [n (%)]	115 (69.7%)	5 (33.3%)	**0.22 (0.07 - 0.67)**	**0.008**
APH in marginal abruption [n (%)]	14 (8.5%)	4 (26.7%)	**3.92 (1.10 - 13.95)**	**0.048**
Gestational age of first episode of bleeding (w) [median (IQR)]	30.0 (3.6)	31.6 (2.9)	**1.41 (1.07 - 1.86)**	**0.008**
Spotting [n (%)]	75 (45.5%)	4 (26.7%)	0.44 (0.13 - 1.43)	0.185
Minor bleeding [n (%)]	64 (38.8%)	6 (40.0%)	1.05 (0.36 - 3.10)	1.000
Major bleeding [n (%)]	26 (15.8%)	5 (33.3%)	2.67 (0.84 - 8.46)	0.143
Duration of the first episode (days) [median (IQR)]	1.0 (1.0)	1.0 (1.0)	1.15 (0.45 - 2.91)	0.578
Duration of the hospitalization (days) [median (IQR)]	7.0 (6.0)	4.0 (3.0)	**0.73 (0.59 - 0.91)**	**0.000**
Cervical length (mm) [median (IQR)]	36.0 (12.0)	35.0 (8.0)	0.98 (0.91 - 1.05)	0.692
Intrauterine growth restriction [n (%)]	8 (4.8%)	4 (26.7%)	**7.14 (1.86 - 27.44)**	**0.011**
Previous preterm delivery [median (IQR)]	0.0 (0.0)	0.0 (0.0)	2.20 (0.52 - 9.38)	0.175
Gestational age at delivery (weeks) [median (IQR)]	37.0 (4.0)	32.3 (3.1)	**0.61 (0.49 - 0.76)**	**0.000**

Data are presented as n (%) or median (IQR)

Table 6. Univariate analysis to delivery within 48 hours of hospitalization in subgroup "APH before 34 WG". (N = 206)

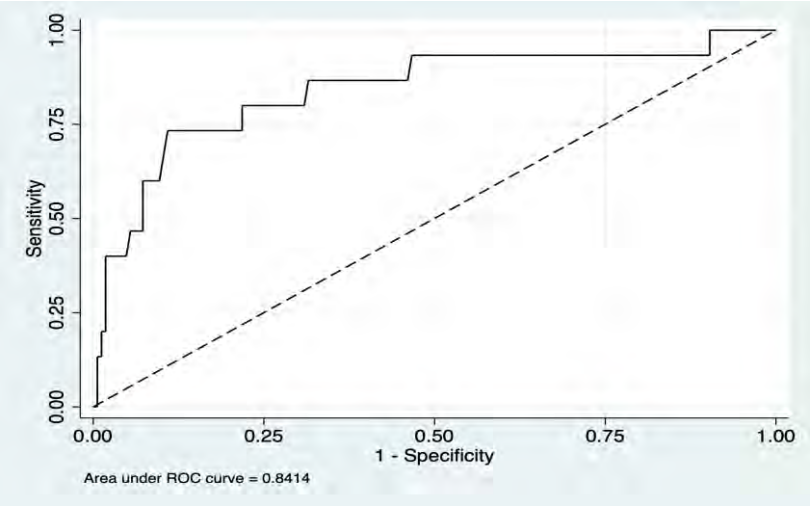
	Delivery within 48 hours of hospitalization		OR (CI 95%)	p-value
	No	Yes		
	N = 202	N = 4		
AHUO [n (%)]	54 (26.7%)	1 (25.0%)	0.91 (0.09 - 8.97)	1.000
APH in placenta previa [n (%)]	135 (66.8%)	1 (25.0%)	0.17 (0.02 - 1.62)	0.115
APH in marginal abruption [n (%)]	18 (8.9%)	2 (50.0%)	**10.22 (1.36 - 76.97)**	**0.048**
Gestational age of first episode of bleeding (w) [median (IQR)]	30.3 (3.3)	32.9 (1.9)	**2.39 (1.04 - 5.46)**	**0.023**
Spotting [n (%)]	88 (43.6%)	1 (25.0%)	0.43 (0.04 - 4.22)	0.635
Minor bleeding [n (%)]	83 (41.1%)	2 (50.0%)	1.43 (0.20 - 10.38)	1.000
Major bleeding [n (%)]	31 (15.3%)	1 (25.0%)	1.84 (0.19 - 18.25)	0.494
Duration of the first episode (days) [median (IQR)]	1.0 (1.0)	1.0 (0.0)	N/A	0.289
Cervical length (mm) [median (IQR)]	35.5 (11.0)	36.0 (14.5)	0.97 (0.86 - 1.08)	0.546
Intrauterine growth restriction [n (%)]	11 (5.4%)	1 (25.0%)	5.79 (0.56 - 60.29)	0.215
Previous preterm delivery [median (IQR)]	0.0 (0.0)	0.0 (0.0)	N/A	0.635
Gestational age at delivery (weeks) [median (IQR)]	36.8 (4.6)	33.1 (1.9)	**0.74 (0.55 - 0.99)**	**0.030**

Data are presented as n (%) or median (IQR)

N/A: not analyzable

Figure 5. Multivariate analysis according to delivery within 7 days of hospitalization in subgroup “APH before 34 WG”. (N = 180)

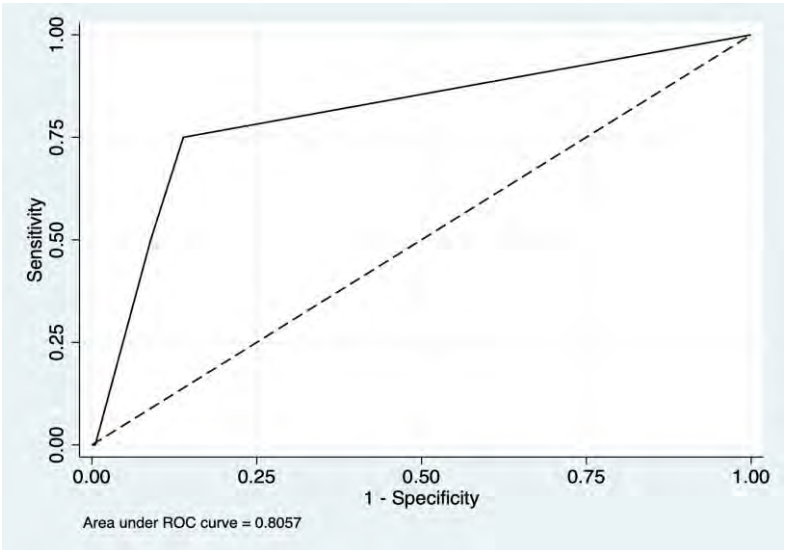
PREDICTIVE CAPACITY OF A MODEL INCLUDING THE ABOVEMENTIONED VARIABLES
AUC = 0.84 (CI 95% 0.72 - 0.97)



VARIABLE	OR (CI 95%)	P-VALUE
Intrauterine growth restriction	9.62 (2.10 - 43.99)	0.004
APH in placenta previa	0.17 (0.05 - 0.65)	0.009
Quantity of bleeding	2.98 (1.30 - 6.82)	0.010
Gestational age of first episode of bleeding (days)	1.05 (1.00 - 1.10)	0.039

Figure 6. Multivariate analysis according to delivery within 48 hours of hospitalization in subgroup “APH before 34 WG”. (N = 206)

PREDICTIVE CAPACITY OF A MODEL INCLUDING THE ABOVEMENTIONED VARIABLES
AUC = 0.81 (CI 95% 0.56 - 1.00)



VARIABLE	OR (CI 95%)	P-VALUE
APH in marginal abruption	25.60 (2.13 - 307.30)	0.011
Intrauterine growth restriction	21.33 (1.19 - 383.93)	0.038

Discussion

In this study of 300 women hospitalized for APH during the third trimester, our results emphasize that APH are associated with significant maternal and fetal morbidity, particularly in the case of placenta previa or marginal abruption, with a higher rate of preterm birth, a reduction of birth weight, and a higher rate of postpartum hemorrhage (and therefore transfusion).

In multivariate analysis, we identified independent factors that could predict delivery within 7 days and 48 hours. We have created prediction models that remain imperfect and should be interpreted with caution. The variables analyzed should be considered as risk factors rather than real predictive factors.

In the subgroup analysis of "APH before 34 WG", we can see that APH related to placenta previa were associated with a lower risk of delivery within 7 days (OR 0.17 (0.05 - 0.65) p = 0.009). On the other hand, whether in the analysis of all patients or in the subgroup "women hospitalized before 34 WG", the amount of bleeding on admission, the gestational age at the time of the first bleeding episode and the presence of IUGR would appear to be risk factors for delivery within 7 days.

The low rate of delivery within 7 days in cases of APH related to placenta previa may be explained by the fact that placenta previa is associated with a high risk of having at least one bleeding episode during pregnancy. However, in most cases, the initial situation is stabilized, and therefore the risk of delivering within 7 days is very low.

Therefore, if it is the first episode of bleeding and the initial situation has stabilized, the risk of cataclysmic hemorrhage remains low, which really raises questions of the value of hospitalization.

We also found that the presence of AHUO is not associated with a risk of delivery within 48 hours (OR 0.19 (0.04-0.94) p = 0.042). On the other hand, in the subgroup analysis of “APH before 34 WG”, we found that APH related to a marginal abruption and the presence of IUGR were factors statistically associated with a risk of delivery within 48 hours. Advanced gestational age was found to be a factor significantly associated with a risk of delivery within

48 hours in the analysis of all patients, but not found in the subgroup analysis of “women hospitalized before 34 WG”.

In fact, the advanced gestational age at the time of APH as a risk factor for delivery within 7 days or 48 hours may simply be explained by the fact that it is more acceptable to induce delivery at an advanced term than when there is a risk of high prematurity. We thus performed this subgroup analysis among women presenting APH before 34WG.

Looking at the overall maternal and fetal outcomes, AHUO seems to have more favorable outcomes. Indeed, in the survival curves (Figure 6 and Figure 11), considering the different potential confounding factors (gestational age at first episode, number of recurrences, duration of first episode, history of preterm delivery), AHUO is associated with a lower risk of preterm birth compared to other causes of APH.

Our results highlight that among women who delivered at term (after 37 WG), a significant proportion (41.8%) received antenatal corticosteroid therapy for fetal lung maturation. While the benefits of antenatal corticosteroid therapy in preventing the risks associated with preterm delivery are unquestionable in early preterm birth, several studies reported that antenatal corticosteroid therapy is associated with an increased risk of neurodevelopmental disorders in exposed children, particularly when they are born at term. (27) Notably, the MACS-5 study in 2014, shows that the rate of death and severe impairments (neuro-motor, neuro-sensory, and neuro-cognitive) was significantly more frequent in the group of children born at term who received multiple doses of corticosteroids during pregnancy, compared to the group of children born at term who did not receive steroids. (28)

Regarding the optimal indications and duration of hospitalization for APH in the third trimester, the results differ in the literature.

O. Ogueh et al reported that hospitalization for AHUO confers no benefit in terms of gestational age at delivery, birth weight, Apgar score, recurrence of bleeding, and that the length of stay was not significantly related to gestational age at delivery or to birth weight or Apgar score. (23)

In contrast, according to G. Roberts, perinatal mortality in cases of AHUO was higher than in the placenta previa group. Also, preterm labor began within 7 days of the onset of bleeding in

the majority of cases of AHUO that resulted in perinatal death. But this is an old study from 1970, therefore, diagnostic performances were not as good as nowadays. (24)

Regarding the association between APH and preterm birth, several studies have already examined this association and their results were similar.

About AHUO, numerous studies have shown that the occurrence of AHUO was associated with a significantly higher risk of preterm delivery and therefore of reduced birth weight. (5–9)

About APH related to placenta previa, two large retrospective studies of women with placenta previa have proposed scores to predict the risk of preterm delivery and emergency cesarean section.

The first study (n = 250) found that the risk was increased if the first episode of bleeding occurred before 29 WG (OR 2.64, 95% CI 1.17-5.98), and if three or more episodes of bleeding occurred (OR 2.53, 95% CI 1.1-5.86). (29)

The second study (n = 214) found that independent predictors of emergency cesarean section were a history of cesarean section (OR 4.7, 95% CI 1.2-12); antepartum hemorrhage on one (OR 7.5, 95% CI 2.5-23), two (OR 14, 95% CI 4.3-47), and three or more occasions (OR 27, 95% CI 8.3-90); and the need for prenatal blood transfusion (OR 6.4, 95% CI 1. 7-23). The risk of preterm delivery by emergency cesarean section thus increased with the number of antepartum bleeding episodes, with one (OR 7.5, 95% CI 2.5-23), two (OR 14, 95% CI 4.3-47), and three or more (OR 27, 95% CI 8.3-90). (30)

The results of these studies suggest that predictors of emergency cesarean section in women with placenta previa can be used to individualize prenatal care with respect to the need for hospitalization, administration of corticosteroids, and timing of delivery.

The results of our study, combined with the above-mentioned publications, indicate that in the setting of APH during third trimester, some factors are associated with a higher risk of delivery within 7 days, such as marginal abruption, IUGR, number of recurrences, quantity of bleeding… and therefore, in the absence of these risk factors, if this is a single episode of bleeding and the situation is stable, it seems reasonable not to prolong the hospitalization and not to carry out the antenatal corticotherapy.

The results of our study may have implications for clinical practice. Indeed, since the risk of delivery within 7 days is low in the placenta previa group which represent the majority of patients, it suggests that there are no argument for a systematic prolonged hospitalization, and rather provide individual care. However, there is still a significant proportion of patients who give birth within 48 hours, so it seems safe to allow to go home after 48 hours if the situation is stable and without other risk factors (major bleeding, presence of IUGR, advanced gestational age at the time of the episode, number of recurrences greater than or equal to 1).

In the same way, because of the low rate of delivery within 48 hours in the case of AHUO, non-routine hospitalization of these patients could be considered, in the absence of other risk factors and if the bleeding has stopped.

The main strengths of our study are, first, the large number of pregnant women with APH with a considerable set of available variables. In addition, the inclusion period of our study is relatively large and with no change in practices during the inclusion period.

On the other hand, the literature is poor on the subject, there are few studies analyzing the benefits of hospitalization and in particular the duration of hospitalization adapted to cases of APH related to placenta previa, or to a marginal abruption or unexplained cause. There are no specific international guidelines about the management of APH on the third trimester.

In addition, our study allows us to extrapolate the need for antenatal corticosteroid therapy and to try to reduce their prescriptions in cases of high probability of term delivery.

The weaknesses of our study are related to its retrospective design, with the possibility of bias inherent in this type of study.

Secondly, our study includes many lost to follow-up (transfer to a lower-level maternity hospital, delivery in another maternity hospital), which reduces the power of the study in the analysis of delivery outcomes.

Finally, the conduct of our study in a single level 3 center raises a possible recruitment bias and limits the variation in practices in the management of APH, which could have an impact on the generalization of the results.

Conclusion

In conclusion, APH are associated with significant maternal and fetal morbidity, particularly in the case of placenta previa or marginal abruption, indeed, AUOH seems to have more favorable outcomes with a low rate of delivery within 7 days or 48 hours. However, the presence of APH related to placenta previa does not seem to increase the risk of delivery within 7 days, but there is a significant proportion of women who give birth within 48 hours. In fact, there are other independent risk factors that should be considered to assess this risk (number of recurrences, quantity of bleeding, gestational age).

Therefore, it could be interesting to individualize prenatal care for APH (duration of hospitalization, administration of corticosteroids), according to the presence of a combination of risk factors.

Further prospective studies are needed to confirm our results and better define the optimal management strategies for third trimester APH according to etiology.

Vu et permis d'imprimer
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Appendix

Table 7. Univariate analysis according to delivery before term (< 37w). N = 250.

	Delivery before term (< 37w)		OR (CI 95%)	p-value
	No	Yes		
	N = 141	N = 109		
AHUO [n (%)]	72 (51.1%)	17 (15.6%)	**0.18 (0.10 - 0.33)**	**0.000**
APH in placenta previa [n (%)]	65 (46.1%)	78 (71.6%)	**2.94 (1.73 - 5.01)**	**0.000**
APH in marginal abruption [n (%)]	7 (5.0%)	16 (14.7%)	**3.29 (1.30 - 8.32)**	**0.014**
Gestational age of first episode of bleeding (w) [median (IQR)]	32.7 (5.4)	31.1 (4.7)	**0.87 (0.80 - 0.94)**	**0.000**
Spotting [n (%)]	80 (56.7%)	34 (31.2%)	**0.35 (0.20 - 0.58)**	**0.000**
Minor bleeding [n (%)]	48 (34.0%)	47 (43.1%)	1.47 (0.88 - 2.46)	0.151
Major bleeding [n (%)]	13 (9.2%)	28 (25.7%)	**3.40 (1.67 - 6.95)**	**0.001**
Duration of the first episode (days) [median (IQR)]	1.0 (0.0)	1.0 (1.0)	**3.01 (1.65 - 5.51)**	**0.000**
Duration of the hospitalization (days) [median (IQR)]	5.0 (5.0)	7.0 (9.0)	**1.11 (1.05 - 1.17)**	**0.001**
Number of recurrences after the first episode [median (IQR)]	0.0 (1.0)	1.0 (2.0)	**1.77 (1.33 - 2.34)**	**0.000**
Cervical length (mm) [median (IQR)]	35.0 (10.0)	35.0 (14.0)	0.99 (0.96 - 1.03)	0.731
Intrauterine growth restriction [n (%)]	3 (2.1%)	10 (9.2%)	**4.65 (1.25 - 17.32)**	**0.019**
Number of previous deliveries [median (IQR)]	1.0 (1.0)	1.0 (2.0)	1.10 (0.88 - 1.38)	0.664
Previous preterm delivery [median (IQR)]	0.0 (0.0)	0.0 (0.0)	**3.02 (1.06 - 8.60)**	**0.035**
Presence of vasa previa [n (%)]	2 (1.4%)	8 (7.3%)	**5.50 (1.14 - 26.47)**	**0.023**
Antenatal corticosteroids [n (%)]	59 (41.8%)	85 (78.0%)	**4.92 (2.80 - 8.65)**	**0.000**
Administered doses of Corticosteroids [median (IQR)]	0.0 (2.0)	2.0 (0.0)	**2.20 (1.66 - 2.91)**	**0.000**

Data are presented as n (%) or median (IQR)

Table 8. Univariate analysis according to delivery before 34w. (N = 256)

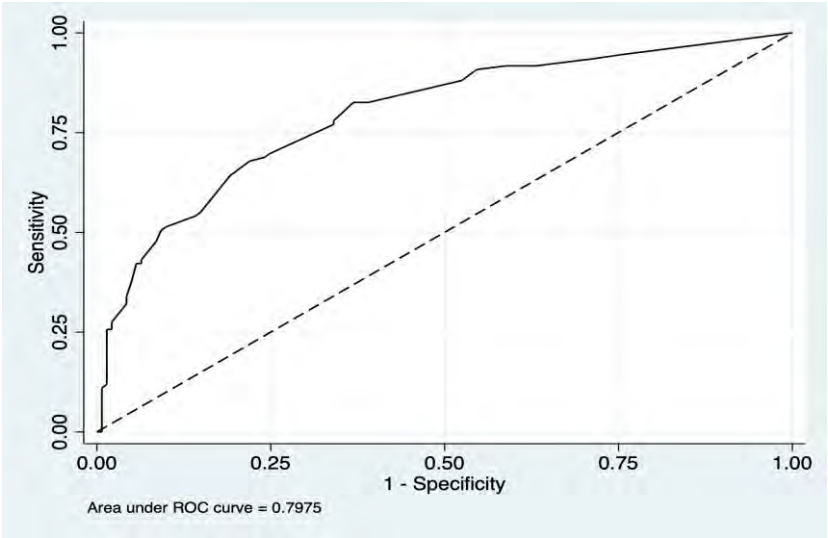
	Delivery before 34w		OR (CI 95%)	p-value
	No	Yes		
	N = 207	N = 49		
AHUO [n (%)]	83 (40.1%)	10 (20.4%)	**0.38 (0.18 - 0.81)**	**0.013**
APH in previa placenta [n (%)]	116 (56.0%)	29 (59.2%)	1.14 (0.60 - 2.14)	0.750
APH in marginal abruption [n (%)]	11 (5.3%)	12 (24.5%)	**5.78 (2.37 - 14.08)**	**0.000**
Gestational age of first episode of bleeding (w) [median (IQR)]	32.6 (5.3)	29.3 (4.3)	**0.80 (0.72 - 0.88)**	**0.000**
Spotting [n (%)]	103 (49.8%)	13 (26.5%)	**0.36 (0.18 - 0.73)**	**0.004**
Minor bleeding [n (%)]	74 (35.7%)	24 (49.0%)	1.73 (0.92 - 3.23)	0.103
Major bleeding [n (%)]	30 (14.5%)	12 (24.5%)	1.91 (0.90 - 4.08)	0.131
Duration of the first episode (days) [median (IQR)]	1.0 (0.0)	1.0 (1.0)	**3.31 (1.82 - 6.02)**	**0.000**
Duration of the hospitalization (days) [median (IQR)]	6.0 (5.0)	6.0 (6.0)	1.01 (0.98 - 1.04)	0.259
Number of recurrences after the first episode [median (IQR)]	0.0 (1.0)	1.0 (1.0)	1.18 (0.99 - 1.41)	**0.003**
Cervical length (mm) [median (IQR)]	35.0 (10.5)	33.0 (12.0)	0.97 (0.93 - 1.02)	0.353
Intrauterine growth restriction [n (%)]	7 (3.4%)	6 (12.2%)	**3.99 (1.28 - 12.45)**	**0.021**
Number of previous deliveries [median (IQR)]	1.0 (1.0)	1.0 (2.0)	**1.33 (1.03 - 1.72)**	**0.034**
Previous preterm delivery [median (IQR)]	0.0 (0.0)	0.0 (0.0)	2.23 (0.83 - 5.97)	0.195
Presence of vasa previa [n (%)]	10 (4.8%)	0 (0.0%)	N/A	0.216
Antenatal corticosteroids [n (%)]	102 (49.3%)	42 (85.7%)	**6.18 (2.65 - 14.38)**	**0.000**
Administered doses of Corticosteroids [median (IQR)]	0.0 (2.0)	2.0 (0.0)	**2.40 (1.59 - 3.62)**	**0.000**

Data are presented as n (%) or median (IQR)

N/A: not analyzable

Figure 7. Multivariate analysis according to delivery before term (< 37 WG) (N = 250)

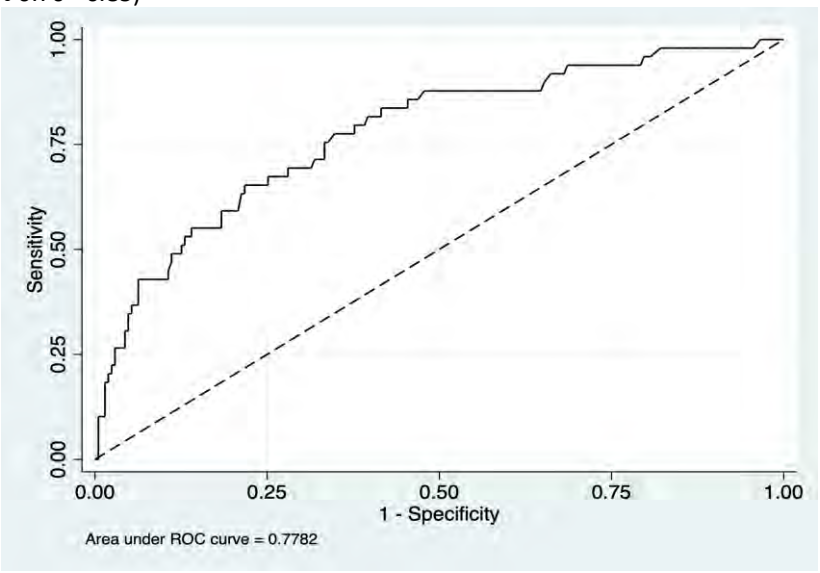
PREDICTIVE CAPACITY OF A MODEL INCLUDING THE ABOVEMENTIONED VARIABLES
AUC = 0.80 (CI 95% 0.74 - 0.85)



VARIABLE	OR (CI 95%)	P-VALUE
AHUO	0.29 (0.15 - 0.57)	0.000
Quantity of bleeding	1.82 (1.20 - 2.75)	0.005
Number of recurrences after the first episode	1.51 (1.13 - 2.01)	0.005
Intrauterine growth restriction	7.02 (1.65 - 29.90)	0.008
Duration of the first episode (days)	2.06 (1.08 - 3.91)	0.028

Figure 8. Multivariate analysis according to delivery before 34 WG (N = 256)

PREDICTIVE CAPACITY OF A MODEL INCLUDING THE ABOVEMENTIONED VARIABLES
AUC = 0.78 (CI 95% 0.70 - 0.85)



VARIABLE	OR (CI 95%)	P-VALUE
Gestational age of first episode of bleeding (days)	0.97 (0.96 - 0.99)	0.000
Duration of the first episode (days)	2.49 (1.33 - 4.65)	0.004
Quantity of bleeding	1.70 (1.06 - 2.70)	0.027
Intrauterine growth restriction	3.60 (1.06 - 12.26)	0.040

Table 9. Univariate analysis according to delivery before term (< 37 WG) in subgroup "APH before 34 WG". (N = 166)

	DELIVERY BEFORE TERM (< 37W)		OR (CI 95%)	P-VALUE
	NO N = 79	YES N = 87		
AHUO [n (%)]	38 (48.1%)	8 (9.2%)	**0.11 (0.05 - 0.26)**	**0.000**
APH IN PLACENTA PREVIA [n (%)]	39 (49.4%)	68 (78.2%)	**3.67 (1.87 - 7.20)**	**0.000**
APH IN MARGINAL ABRUPTION [n (%)]	5 (6.3%)	13 (14.9%)	2.60 (0.88 - 7.66)	0.085
GESTATIONAL AGE OF FIRST EPISODE OF BLEEDING (W) [median (IQR)]	30.3 (3.9)	29.9 (3.6)	0.95 (0.84 - 1.08)	0.472
SPOTTING [n (%)]	47 (59.5%)	25 (28.7%)	**0.27 (0.14 - 0.52)**	**0.000**
MINOR BLEEDING [n (%)]	24 (30.4%)	40 (46.0%)	**1.95 (1.03 - 3.69)**	0.055
MAJOR BLEEDING [n (%)]	8 (10.1%)	22 (25.3%)	**3.00 (1.25 - 7.22)**	**0.015**
DURATION OF THE FIRST EPISODE (DAYS) [median (IQR)]	1.0 (0.0)	1.0 (1.0)	**3.28 (1.59 - 6.76)**	**0.001**
DURATION OF THE HOSPITALIZATION (DAYS) [median (IQR)]	6.0 (5.0)	7.0 (10.0)	**1.14 (1.06 - 1.23)**	**0.000**
NUMBER OF RECURRENCES AFTER THE FIRST EPISODE [median (IQR)]	0.0 (1.0)	1.0 (2.0)	**1.61 (1.19 - 2.16)**	**0.000**
CERVICAL LENGTH (MM) [median (IQR)]	36.0 (11.5)	35.0 (13.0)	0.98 (0.94 - 1.02)	0.315
INTRAUTERINE GROWTH RESTRICTION [n (%)]	3 (3.8%)	9 (10.3%)	2.92 (0.76 - 11.21)	0.137
NUMBER OF PREVIOUS DELIVERIES [median (IQR)]	1.0 (1.0)	1.0 (2.0)	1.17 (0.90 - 1.51)	0.231
PREVIOUS PRETERM DELIVERY [median (IQR)]	0.0 (0.0)	0.0 (0.0)	1.95 (0.53 - 7.14)	0.300
PRESENCE OF VASA PREVIA [n (%)]	2 (2.5%)	8 (9.2%)	3.90 (0.80 - 18.95)	0.103
ANTENATAL CORTICOSTEROIDS [n (%)]	57 (72.2%)	83 (95.4%)	**8.01 (2.62 - 24.48)**	**0.000**
ADMINISTERED DOSES OF CORTICOSTEROIDS [median (IQR)]	2.0 (2.0)	2.0 (0.0)	**2.70 (1.57 - 4.63)**	**0.000**

Data are presented as n (%) or median (IQR)

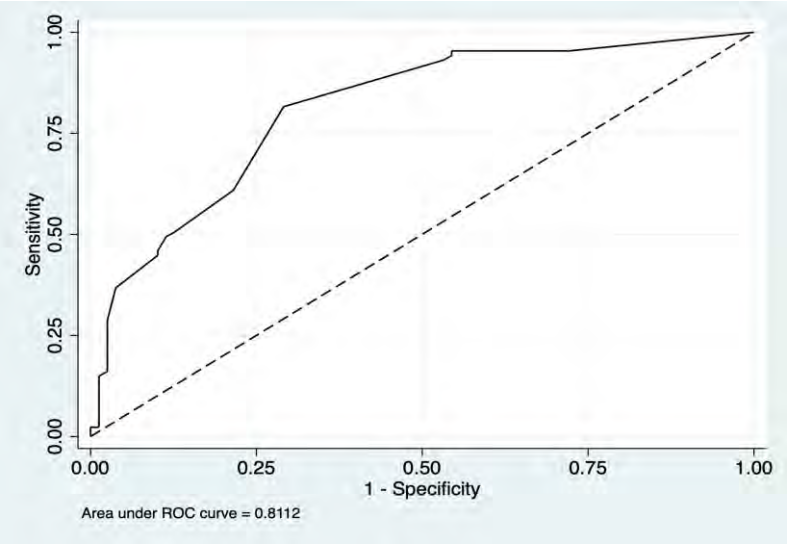
Table 10. Univariate analysis according to delivery before 34 WG in subgroup "APH before 34 WG". (N = 167)

	DELIVERY BEFORE 34W		OR (CI 95%)	P-VALUE
	NO N = 123	YES N = 44		
AHUO [n (%)]	40 (32.5%)	6 (13.6%)	**0.33 (0.13 - 0.84)**	**0.018**
APH IN PLACENTA PREVIA[n (%)]	80 (65.0%)	28 (63.6%)	0.94 (0.46 - 1.93)	0.857
APH IN MARGINAL ABRUPTION [n (%)]	6 (4.9%)	12 (27.3%)	**7.31 (2.55 - 21.00)**	**0.000**
GESTATIONAL AGE OF FIRST EPISODE OF BLEEDING (W) [median (IQR)]	30.3 (3.7)	29.0 (4.5)	0.87 (0.75 - 1.00)	0.050
SPOTTING [n (%)]	61 (49.6%)	11 (25.0%)	**0.34 (0.16 - 0.73)**	**0.005**
MINOR BLEEDING [n (%)]	43 (35.0%)	22 (50.0%)	1.86 (0.93 - 3.74)	0.105
MAJOR BLEEDING [n (%)]	19 (15.4%)	11 (25.0%)	1.82 (0.79 - 4.22)	0.173
DURATION OF THE FIRST EPISODE (DAYS) [median (IQR)]	1.0 (0.0)	1.5 (1.0)	**3.13 (1.61 - 6.07**	**0.000**
DURATION OF THE HOSPITALIZATION (DAYS) [median (IQR)]	7.0 (6.0)	6.5 (7.5)	0.99 (0.96 - 1.02)	0.600
NUMBER OF RECURRENCES AFTER THE FIRST EPISODE [median (IQR)]	0.0 (1.0)	1.0 (2.0)	1.08 (0.90 - 1.29)	0.427
CERVICAL LENGTH (MM) [median (IQR)]	36.0 (12.0)	32.0 (13.0)	0.96 (0.92 - 1.00)	0.064
INTRAUTERINE GROWTH RESTRICTION [n (%)]	6 (4.9%)	6 (13.6%)	3.08 (0.94 - 10.11)	0.083
NUMBER OF PREVIOUS DELIVERIES [median (IQR)]	1.0 (1.0)	1.0 (2.0)	1.32 (1.00 - 1.73)	**0.043**
PREVIOUS PRETERM DELIVERY [median (IQR)]	0.0 (0.0)	0.0 (0.0)	**3.69 (1.05 - 13.02)**	**0.024**
PRESENCE OF VASA PREVIA [n (%)]	10 (8.1%)	0 (0.0%)	N/A	0.064
ANTENATAL CORTICOSTEROIDS [n (%)]	98 (79.7%)	42 (95.5%)	**5.36 (1.21 - 23.65)**	**0.016**
ADMINISTERED DOSES OF CORTICOSTEROIDS [median (IQR)]	2.0 (0.0)	2.0 (0.0)	**2.08 (1.05 - 4.11)**	**0.024**

Data are presented as n (%) or median (IQR)

Figure 9. Multivariate analysis according to delivery before term (< 37 WG) in subgroup "APH before 34 WG". (N = 206)

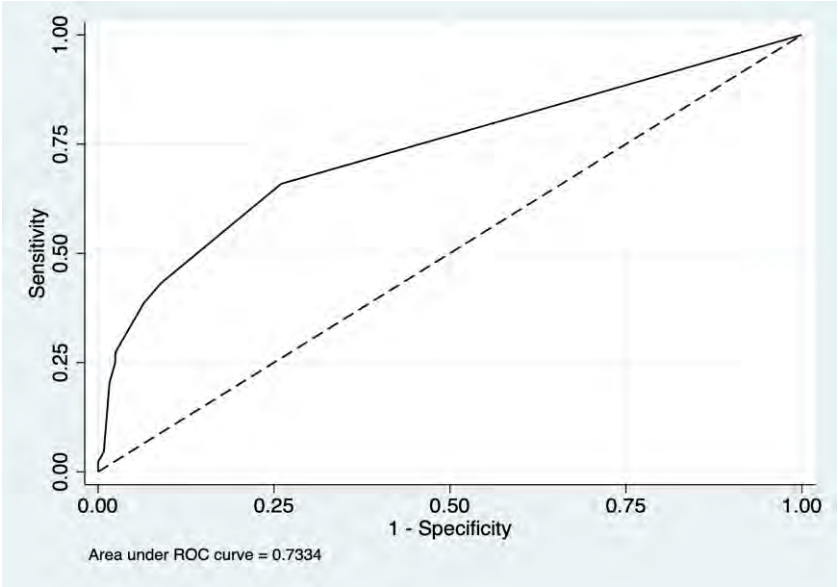
PREDICTIVE CAPACITY OF A MODEL INCLUDING THE ABOVEMENTIONED VARIABLES
AUC = 0.81 (CI 95% 0.75 - 0.88)



VARIABLE	OR (CI 95%)	P-VALUE
AHUO	0.12 (0.04 - 0.31)	0.000
Duration of the first episode (days)	3.17 (1.39 - 7.22)	0.006
Intrauterine growth restriction	5.96 (1.25 - 28.49)	0.025
Number of recurrences after the first episode	1.34 (1.00 - 1.80)	0.047

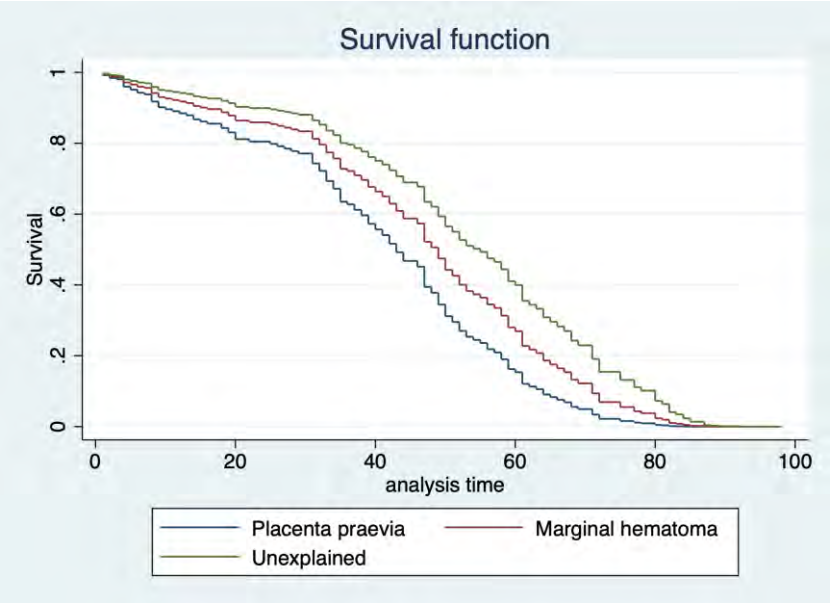
Figure 10. Multivariate analysis according to delivery before 34 WG in subgroup "APH before 34 WG". (N = 167)

PREDICTIVE CAPACITY OF A MODEL INCLUDING THE ABOVEMENTIONED VARIABLES
AUC = 0.73 (CI 95% 0.65 - 0.82)



VARIABLE	OR (CI 95%)	P-VALUE
APH in marginal abruption	8.05 (2.68 - 24.15)	0.000
Duration of the first episode (days)	2.85 (1.46 - 5.54)	0.002
Previous preterm delivery	4.58 (1.16 - 18.18)	0.030

Figure 11. Survival analysis : time from admission until delivery using cause bleeding in subgroup “APH before 34 WG”.



VARIABLE	HR (CI 95%)	P-VALUE
Gestational age of first episode of bleeding (days)	1.06 (1.05 - 1.07)	0.000
Cause of the bleeding	0.70 (0.58 - 0.85)	0.000
Intrauterine growth restriction	2.12 (1.16 - 3.86)	0.014
Number of recurrences after the first episode	1.12 (1.03 - 1.21)	0.010
Duration of the first episode (days)	1.59 (1.21 - 2.09)	0.001
Previous preterm delivery	1.94 (1.04 - 3.60)	0.037

Table 11. Hospitalization length according to the cause of bleeding
Outcome: Delivery before term (< 37 SA)

	Delivery before term (< 37w)			
	No	Yes	OR (CI 95%)	p-value
Duration of the hospitalization placenta previa (days) [median (IQR)]	N = 62 7.0 (2.0)	N = 76 7.0 (9.0)	**1.09 (1.03 - 1.15)**	0.063[3]
Duration of the hospitalization marginal hematoma (days) [median (IQR)]	N = 7 7.0 (6.0)	N = 16 3.5 (8.5)	1.00 (0.89 - 1.13)	0.295[3]
Duration of the hospitalization AHUO (days) [median (IQR)]	N = 72 2.0 (1.0)	N = 17 2.0 (1.0)	0.91 (0.67 - 1.23)	0.643[3]

Table 12. Hospitalization length according to the cause of bleeding
Outcome: Delivery before 34 SA

	Delivery before 34w			
	No	Yes	OR (CI 95%)	p-value
Duration of the hospitalization placenta previa(days) [median (IQR)]	N = 113 7.0 (4.0)	N = 27 7.0 (9.0)	1.00 (0.96 - 1.04)	0.791[3]
Duration of the hospitalization marginal hematoma (days) [median (IQR)]	N = 11 7.0 (7.0)	N = 12 3.5 (8.5)	0.97 (0.87 - 1.09)	0.554[3]
Duration of the hospitalization AHUO (days) [median (IQR)]	N = 83 2.0 (1.0)	N = 10 3.0 (3.0)	1.14 (0.86 - 1.51)	0.143[3]

Serment d'Hippocrate

«Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leur raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime
si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.»

Summary

GAUGRY Maurine 2022 TOU3 1563

ANTEPARTUM HEMORRHAGE: FACTORS ASSOCIATED WITH ADVERSE MATERNAL AND FETAL OUTCOMES

OBJECTIF : To evaluate the factors associated with a delivery within 7 days in case of APH between 24 and 37 weeks of gestation, according to the etiology. Secondly, we will analyze perinatal outcomes according to the etiology of APH.

METHODS : This is a retrospective cohort study conducted in the Paule de Viguier maternity hospital of Toulouse from January 1, 2015, to December 31, 2019. All women hospitalized for a first episode of APH, not requiring immediate emergency delivery, between 24 WG and 37 WG, were included. The primary outcome was defined as any delivery occurring within 7 days of hospitalization. Secondary outcomes were defined as deliveries within 48 hours of hospitalization and they also included neonatal and maternal outcomes.

RESULTS : In this study of 300 women hospitalized for APH during the third trimester, APH are associated with significant maternal and fetal morbidity, particularly in the case of placenta previa or marginal abruption. In the subgroup of women presenting APH before 34 WG, APH related to placenta previa were associated with a lower risk of delivery within 7 days (OR 0.17 (0.05 - 0.65) p = 0.009). On the other hand, the amount of bleeding on admission, the gestational age at the first bleeding episode and the presence of IUGR would appear to be risk factors for delivery within 7 days. Also, AHUO is not associated with a risk of delivery within 48 hours (OR 0.19 (0.04-0.94) p = 0.042). In the subgroup women presenting APH before 34 WG, APH related to a marginal abruption and the presence of IUGR were factors statistically associated with a risk of delivery within 48 hours (respectively OR 25.6 (2.3 – 307.30) p = 0.011 and OR 21.33 (1.19 – 383.93) p = 0.038).

CONCLUSION : Even if AHUO is associated with more favorable outcomes, the risk of delivery within 7 days is low in the placenta previa group. Therefore, there are no arguments for a systematic prolonged hospitalization in cases of placenta previa, and rather provide individual care based on other additional risk factors.

DISCIPLINE ADMINISTRATIVE : Médecine spécialisée clinique, Gynécologie-obstétrique

MOTS-CLÉS : Antepartum hemorrhage of unknown origin, placenta previa, marginal abruption, hospitalization

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