Open Journal of Obstetrics and Gynecology, 2016, 6, 107-116
Published Online February 2016 in SciRes. http://www.scirp.org/journal/ojog
http://dx.doi.org/10.4236/ojog.2016.62013

Late Antepartum Hemorrhage and Neonatal Outcome: A Retrospective Study

Panagiotis Tsikouras*, Zacharoula Koukouli, Anastasios Liberis, Bachar Manav, Constantinos Bouschanetzis, Panagiotis Naoumis, Marina Dimitraki, Georgios Galazios

Department of Obstetrics and Gynecology, Democritus University of Thrace, Alexandroupoli, Greece
Email: *ptsikour@med.duth.gr

Received 13 January 2016; accepted 14 February 2016; published 17 February 2016

Abstract

Objective: To retrospectively evaluate the causes, the management and neonatal outcome in pregnancies complicated with late antepartum hemorrhage (APH), defined as vaginal bleeding during the third trimester of pregnancy. Methods: We retrospectively identified all eligible patients at a single institution from January 1990 to December 2012. A thorough research was made through patients' medical and obstetrical records. The various causes of late APH were compared to each other regarding the parameters of the neonatal outcome. Multiple regression models were applied for gestational age (GA) at birth, birth weight, Apgar score at first and fifth minute and selection of modus of delivery. Results: 480 patients were included in the study, in a total of 7221 pregnancies. The causes of APH were: cervical dilatation (*n* = 54, 11.3%), central placental abruption (*n* = 57, 11.9%), peripheral placental abruption (*n* = 59, 12.3%), placenta previa (*n* = 140, 29.2%), others non-related to pregnancy (*n* = 42, 8.8%), uterine rupture (*n* = 2, 0.4%) and unknown etiology (*n* = 126, 26.3%). Overall, 253 neonates (52.7%) were born prematurely at gestational age below 37th week. 37 pregnancies (7.7%) resulted in giving birth prior to 32 weeks of gestation. In multivariable analysis, the cause of hemorrhage was found to be an important independent predictive factor for gestational age (GA) at birth, birth weight, Apgar scores at first and fifth minute and modus of delivery. Preeclampsia, diabetes, thyroid disorder and smoking were associated with decrease of GA at birth. Birth weight below 1500 gr and GA at birth was found to be significant independent factors for Apgar score at first and fifth minute respectively. Modus of delivery did not significantly alter Apgar score. Conclusions: Late APH required immediate evaluation of the general condition of the pregnant woman and the fetus. The cause of APH was important in the prognosis of the neonatal outcome. As long as maternal and fetal status were ensured, expectant management, instead of emergency CS, seemed to be more beneficial even for late preterm neonates.

Keywords

APH, Vaginal Bleeding, Neonatal Outcome, Prognostic Factors

*Corresponding author.

How to cite this paper: Tsikouras, P., Koukouli, Z., Liberis, A., Manav, B., Bouschanetzis, C., Naoumis, P., Dimitraki, M. and Galazios, G. (2016) Late Antepartum Hemorrhage and Neonatal Outcome: A Retrospective Study. *Open Journal of Obstetrics and Gynecology*, **6**, 107-116. http://dx.doi.org/10.4236/ojog.2016.62013

1. Introduction

Antepartum hemorrhage (APH) or late APH is defined as bleeding from the genital tract between 28 completed weeks of pregnancy and the onset of labor [1]. As the placental bed is the commonest site of APH, placenta previa and placental abruption are the leading causes. In a few cases, the etiology of bleeding is found locally in the genital tract (cervicitis, trauma, vaginal varicosities, genital infections, ectropion, polyps, cervical cancer) whereas in a substantial remainder, the bleeding has no obvious cause, probably still deriving from the placental bed [1]. Cervical dilatation during normal labour is also commonly accompanied by an amount of blood [2].

Placental abruption is an important cause of perinatal mortality and morbidity, complicating 1% of pregnancies [3] [4]. The diagnosis of abruption is clinical and refers to the premature separation of the placenta from the uterine wall prior to delivery of the fetus [4] [5]. Risk factors that have been associated with placental abruption include hypertension, substance abuse, smoking, intrauterine infection, recent trauma, prior abruption, multifetal gestation, thrombophilias, advanced maternal age, preterm premature rupture of the membranes and hydramnios [4] [5]. Placenta previa is the second leading cause of vaginal bleeding in the latter half of pregnancy, with an estimated incidence of 0.4% [6]. The term previa is used when the placenta is inserted wholly or in part into the lower segment of the uterus. According to clinical relevance, it is classified by ultrasound: if the placenta lies over the internal cervical os, it is considered a major previa; if the leading edge of the placenta is in the lower uterine segment but not covering the cervical os, minor or partial previa exists [7]. Advancing maternal age, multiparity, previous Cesarean delivery and abortion, smoking, cocaine use and male fetuses have been associated to increased risk for placenta previa [6]. With placenta previa of the perinatal risk, especially preterm delivery, is also high [8]. APH of unknown origin is common, may complicate up to 6% of pregnancies and contributes to 50% of all APH, when ultrasound is used for the exclusion of placental causes [9]-[11]. Preterm delivery and other adverse pregnancy outcomes have been associated with APH of unknown origin [9] [11]-[13].

Unlike placental abruption, placenta previa or even APH of unknown origin, the incidence of vaginal bleeding occurring for the first time during the third trimester of pregnancy is not well documented. According to a study, 15.3% of pregnancies are complicated by APH during the third trimester [14]. Although some studies evaluate the obstetric outcome of first and second trimester antenatal bleeding, current literature on late APH consists of reviews [2] [15] [16] or retrospective studies focusing on specific etiologies [5] [9] [10] [12] [17]-[26]. Studies that include different causes of bleeding and examine the perinatal outcome are lacking [27]. Considering the heterogeneous presentation of third trimester vaginal bleeding in every-day clinical practice, our study aims at a retrospective overview and evaluation of the causes, the management and the perinatal outcome in pregnancies complicated with late APH.

2. Methods

Using the data bank of our Department, we retrospectively identified all women who were treated for APH, regardless of the cause, in a single institution from January 1990 to December 2012. The women included in the study presented with vaginal bleeding for the first time after 27 completed weeks of gestation, and in such amount that demanded admission to the hospital for further evaluation. Pregnant women with multiple pregnancies, congenital anomalies or without spontaneous conception were excluded.

A thorough research was made through patients' medical and obstetrical records. The data collected regard the following: maternal age, parity, previous miscarriage, smoking habit, any pre-pregnancy medical history with drug administration, presence of preeclampsia, thyroid disorder or diabetes, the discharge diagnosis on the cause of bleeding, gestational age (GA) in weeks on admission for APH, GA in weeks at birth, modus of delivery, birth weight and Apgar scores at the first and fifth minute. The discharge diagnosis on the cause of bleeding was based on obstetrical history, clinical presentation, physical examination with a sterile speculum, ultrasonographic evaluation and digital examination. Placental location was determined for all patients by ultrasonography. The diagnosis of suspected uterine rupture was confirmed during caesarean section (CS). When a diagnosis could not be established, the cases were classified as late APH of unknown etiology. All patients had also undergone laboratory testing, including haematocrit, platelet count and coagulation studies. All pregnant women had received at least one intramuscular dose of 12 mg betamethasone immediately after hospital admission, repeated after 24 hours if the pregnancy had not been terminated. A brief period of observation could usually differentiate minor from serious causes of vaginal bleeding.

Following descriptive statistical analysis of the collected data, the various causes of late APH were compared

to each other regarding the parameters of the neonatal outcome. All the comparisons were made using one-way ANOVA, followed by post-hoc tests (with Bonferroni corrections). In a second part of the study an attempt was made to define the critical factors that determine the neonatal outcome in pregnancies complicated with late vaginal bleeding. Multiple regression models were applied for each of the components of the neonatal outcome. As a starting point all the available data were used (mentioned above). All statistical tests were two-sided and the level of statistical significance was set to 0.05. Data analysis was performed using IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY.

3. Results

From January 1990 to December 2012, 480 pregnant women matching the inclusion criteria were treated for late APH regardless of the cause in our institution, in a total of 7221 pregnancies. That corresponds to a rate of 66.4 in 1000 pregnancies. Patients' characteristics and perinatal outcomes are listed in **Table 1**. Overall, 253 neonates (52.7%) were born prematurely at gestational age below 37th week. Furthermore, 37 pregnancies (7.7%) resulted in giving birth prior to 32 weeks of gestation. The causes of APH were: cervical dilatation (n = 54, 11.3%), central placental abruption (n = 57, 11.9%), peripheral placental abruption (n = 59, 12.3%), placenta previa (n = 140, 29.2%), others non related to pregnancy (n = 42, 8.8%), uterine rupture (n = 2, 0.4%) and unknown etiology (n = 126, 26.3%). Perinatal outcomes are presented separately for each cause of bleeding in **Table 2**.

APH due to peripheral placental abruption appeared later in pregnancy (32.9 weeks, 95% CI [32.2, 33.5]) than hemorrhage due to central placental abruption (p-value = 0.037), placenta previa (p-value = 0.016) and unknown reasons (p-value = 0.049). The GA at birth was greater in pregnancies with late vaginal bleeding caused by cervical dilation (mean 37.3 weeks, 95% CI [36.9, 37.8]) than pregnancies complicated with central placental abruption (p-value = 0.00), peripheral placental abruption (p-value = 0.011), and placenta previa (p-value = 0.00). The smallest GA at the time of delivery appeared with central placental abruption (mean 31.7 weeks, 95% CI [31.0, 32.4]), reflecting a significant difference at 5% level with peripheral placental abruption (p-value = 0.00), placenta previa (p-value = 0.00), uterine rupture (p-value = 0.028), causes non related to pregnancy (p-value = 0.00) and unknown etiology bleeding (p-value = 0.00). The last significant difference of the kind was noted between placenta previa and bleeding of unknown etiology (p-value = 0.00). Time interval from admission to delivery in weeks for the two cases of uterine rupture and for the cases of central placental abruption was always 0, unfortunately a more accurate measurement was not available. This fact clinically reflects the urgent character of every hemorrhage attributed to central placental abruption or uterine rupture and statistically results in significant differences at 5% level with every other cause of late APH. As expected, conservative management prevails for bleeding attributed to cervical dilation, (mean time interval from admission to delivery 5.4 weeks, 95% CI [4.9, 5.8]). When compared with other causes of late APH the difference is significant with central placental abruption and uterine rupture (previously commented upon), peripheral placental abruption (p-value = 0.00) and placenta previa (p-value = 0.00). Also vaginal bleeding in late pregnancy that cannot be attributed to a specific cause is managed more expectantly according to the data, with statistically important differences between unknown etiology bleeding and peripheral placental abruption (p-value = 0.00) and placenta previa (p-value = 0.001). The Apgar scores' difference between the various causes of late antepartum bleeding as reported in our study is very small, probably without any clinical significance (an Apgar score less than 7 was not reported in any of the cases). The best Apgar scores at first minute were reported with peripheral placental abruption and placenta previa, resulting in statistically significant differences with central placental abruption (p-value = 0.00), causes non-related to pregnancy (p-value = 0.00) and unknown etiology bleeding (p-value = 0.028). The worst Apgar scores at fifth minute were reported with central placental abruption resulting in statistically significant differences with peripheral placental abruption (p-value = 0.001), placenta previa (p-value = 0.00), causes non-related to pregnancy (p-value = 0.00) and unknown etiology bleeding (p-value = 0.00). Infants with higher birth weight followed pregnancies with late vaginal bleeding attributed to cervical dilatation. The difference in birth weight with other causes of late antepartum bleeding was always significant (p-value = 0.00), with the exception of uterine rupture. Unknown etiology bleeding presented with the second most favorable outcome in terms of birth weight. The difference was significant with placenta previa (p-value = 0.00) and causes non related to pregnancy (p-value = 0.037). The worst neonatal outcome in terms of birth weight came from pregnancies complicated with central placental abruption, resulting in significant differences with every other cause of late APH (p-value = 0.00), with the exception of uterine rupture.

Table 1. Summary of characteristics, gestational age on admission, gestational age at birth, birth weight, Apgar score at first and fifth minute and modus of delivery in 480 cases with late APH, regardless of the cause. Percentages and number of cases (in parentheses) are presented.

Maternal age		
16 - 35 years	76.7%	(368)
>35 years	22.5%	(108)
<16 years	0.8%	(4)
Parity		
I	39.4%	(189)
II - III	54.1%	(260)
IV	6.5%	(31)
Risk factors		
Preeclampsia	22.1%	(106)
Diabetes	6.5%	(31)
Thyroid disorder	4.2%	(20)
Previous medical history	2.9%	(14)
Previous miscarriage	8.1%	(39)
Smoker	27.5%	(132)
Two risk factors	19.6%	(94)
Without risk factors	9.1%	(44)
Gestational age on admission (weeks)		
≤31	37.5%	(180)
32 - 33	40.6%	(195)
34 - 36	20.4%	(98)
>36	1.5%	(7)
Gestational age at birth (weeks)		
<32	7.7%	(37)
32 - 33	12.9%	(62)
34 - 36	32.1%	(154)
≥37	47.3%	(227)
Birth weight (gr)		
≥2500	35.6%	(172)
1500 - 2500	62.7%	(300)
1000 - 1500	1.5%	(7)
500 - 1000	0.2%	(1)
Apgar score at first minute		
7	0.4%	(2)
8	12.9%	(62)
9 - 10	86.7%	(416)
Apgar score at fifth minute		
8	1%	(5)
9 - 10	99%	(475)
Modus of delivery		
Vaginal delivery	15.4%	(74)
Assisted vaginal delivery	25.8%	(124)
Caesarian section	58.8%	(282)

Table 2. Gestational age on admission, gestational age at birth, time from admission to delivery, birth weight and Apgar scores at first and fifth minute according to the cause of the bleeding in 480 cases with late APH.[1] Percentages, number of cases (in parentheses) mean values and 95% CI's of the mean (in brackets) are displayed.

Cause	Fr.	GA on admission (weeks)	GA at birth (weeks)	Time to delivery (weeks)	Birth weight (gr)	Apgar score (at 1')	Apgar score (at 5')
In total	100% (480)	32.0 [31.8, 32.1]	35.7 [35.4, 35.9]	3.7 [3.5, 4.0]	2367 [2327, 2407]	8.87 [8.84, 8.91]	9.73 [9.68, 9.77]
Cervical dilation	11.3% (54)	31.7 [31.3, 32.6]	37.3 [36.9, 37.8]	5.4 [4.9, 5.8]	2754 [2648, 2860]	8.85 [8.75, 8.94]	9.64 [9.51, 9.77]
C. placental abruption	11.9% (57)	32.9 [31.0, 32.4]	31.7 [31.0, 32.4]	0	1855 [1744, 1967]	8.68 [8.54, 8.82]	9.42 [9.25, 9.58]
P. placental abruption	12.3% (59)	32.9 [32.2, 33.5]	36.0 [35.5, 36.5]	3.1 [2.7, 3.5]	2379 [2271, 2487]	9.03 [8.93, 9.13]	9.76 [9.64, 9.88]
Placenta previa	29.2% (140)	31.8 [31.5, 32.1]	35.5 [35.2, 35.9]	3.7 [3.3, 4.0]	2282 [2227, 2338]	8.99 [8.96, 9.02]	9.77 [9.70, 9.84]
Uterine rupture	0.4% (2)	36.5	36.5	0	2645	8.50	9.50
Non-pregnancy	8.8% (42)	31.9 [31.5, 32.3]	36.2 [35.5, 36.8]	4.3 [3.5, 5.0]	2317 [2211, 2424]	8.66 [8.51, 8.81]	9.90 [9.81, 9.99]
Unknown etiology	26.3% 126)	31.9 [31.6, 32.1]	36.8 [36.3, 37.1]	4.8 [4.3, 5.2]	2532 [2459, 2604]	8.84 [8.78, 8.91]	9.79 [9.72, 9.86]

In order to define the prognostic factors for GA (in weeks) at birth, multiple linear regression analysis was used (**Table 3**). When all available data are considered together, important prognostic factors for GA at birth seem to be the cause of the bleeding, in particular cervical dilation (p-value = 0.007, β = 0.63, 95% CI [0.17, 1.09]), central placental abruption (p-value = 0.00, β = −5.06, 95% CI [−5.51, −4.60]), peripheral placental abruption (p-value = 0.00, β = −1.33, 95% CI [−1.78, −0.88]), placenta previa (p-value = 0.00, β = −1.14, 95% CI [−1.49, −0.79]), and causes non related to pregnancy (p-value = 0.045, β = −0.51, 95% CI [−1.02, −0.01]), GA on admission (p-value = 0.00, β = 0.50, 95% CI [0.44, 0.57]), presence of preeclampsia (p-value = 0.00, β = −1.18, 95% CI [−1.69, −0.67]), diabetes (p-value = 0.00, β = −1.11, 95% CI [−1.69, −0.53]), thyroid disorder (p-value = 0.00, β = −1.58, 95% CI [−2.31, −0.84]) and smoking habit (p-value = 0.00, β = −1.00, 95% CI [−1.47, −0.52]). If GA during which the bleeding first occurs is raised by a week, half a week is gained on average for GA at birth, with all the other factors fixed. Under the same premise, when preeclampsia, diabetes, thyroid disorder and smoking habit are present, GA at birth is decreased on average by 1.18, 1.11, 1.58, 1.0 weeks respectively.

In order to define the prognostic factors for birth weight, multiple linear regression analysis was used (**Table 3**). When all available data are considered together, only GA at birth (p-value = 0.00, β = 145.81, 95% CI [135.45, 156.17]) and cause of the bleeding, in particular cervical dilation (p-value = 0.001, β = 127.83, 95% CI [52.01, 203.64]), placenta previa (p-value = 0.006, β = −81.80, 95% CI [−140.04, −23,55] and causes non related to pregnancy (p-value = 0.001, β = −139.22, 95% CI [−222.12, −56.32]) seem to be important prognostic factors for birth weight. Interestingly enough, neither preeclampsia (p-value = 0.38), nor diabetes (p-value = 0.63) were found to be statistically significant independent predictive factors for infant birth weight in pregnancies complicated with APH. With all the other factors fixed, prolongation of pregnancy for a week results on an average increase of 145.81 gr in birth weight.

Multiple linear regression analysis was also applied in an attempt to determine the significant prognostic factors for Apgar scores at first and fifth minute (**Table 3**). For Apgar score at first minute significant independent predictive factors seem to be birth weight below 1500gr (p-value = 0.005, β = −1.04, 95% CI [−1.77, −0.31]), GA on admission (p-value = 0.00, β = 0.03, 95% CI [0.02, 0.05]) and cause of the bleeding, in particular peripheral placental abruption (p-value = 0.01, β = 0.14, 95% CI [0.03, 0.25]), placenta previa (p-value = 0.002, β = 0.13, 95% CI [0.05, 0.22]) and causes non related to pregnancy (p-value = 0.003, β = −0.18, 95% CI [−0.31, −0.06]). GA at delivery is an important independent predictive factor for Apgar score at fifth minute, especially GA below 32 weeks (p-value = 0.00, β = −0.51, 95% CI [−0.71, −0.31]). For these former cases of preterm

[1]APH = antepartum hemorrhage, GA = gestational age, C. placental abruption = central placental abruption, P. placental abruption = peripheral placental abruption, Non-pregnancy = non-pregnancy related causes, Fr. = frequency.

Table 3. Prognostic factors for gestational age at birth, birth weight, Apgar scores at first and fifth minute and selection of modus of delivery (CS) in pregnancies complicated with late APH. Multiple regression analysis.[2]

Gestational age (week) at birth			
	Factor Beta 95% *CI p-value*		
Cervical dilation	0.63	[0.17, 1.09]	0.007
C. placental abruption	−5.06	[−5.51, −4.60]	0.00
P. placental abruption	−1.33	[−1.78, −0.88]	0.00
Placenta previa	−1.14	[−1.49, −0.79]	0.00
Non-pregnancy	−0.51	[−1.02, −0.01]	0.045
GA on admission (weeks)	0.50	[0.44, 0.57]	0.00
Preeclampsia	−1.18	[−1.69, −0.67]	0.00
Diabetes	−1.11	[−1.69, −0.53]	0.00
Thyroid disorder	−1.58	[−2.31, −0.84]	0.00
Smoking	−1.00	[−1.47, −0.52]	0.00
Birth weight			
	Factor Beta 95% *CI p-value*		
Cervical dilation	127.83	[52.01, 203.64]	0.001
Placenta previa	−81.80	[−140.04, −23,55]	0.006
Non-pregnancy	−139,22	[−222.12, −56.32]	0.001
GA at birth (weeks)	145,81	[135.45, 156.17]	0.00
Apgar score at first minute			
	Factor Beta 95% *CI p-value*		
P. placental abruption	0.14	[0.03, 0.25]	0.01
Placenta previa	0.13	[0.05, 0.22]	0.002
Non-pregnancy	−0.18	[−0.31, −0.06]	0.003
Birth weight below 1500 gr.	−1.04	[−1.77, −0.31]	0.005
GA on admission (weeks)	0.03	[0.02, 0.05]	0.00
Apgar score at fifth minute			
	Factor Beta 95% *CI p-value*		
Non-pregnancy	0.31	[0.13, 0.49]	0.00
Unknown etiology	0.16	[0.02, 0.30]	0.02
GA below 32 weeks	−0.51	[−0.71, −0.31]	0.00
Apgar score at first minute	0.20	[0.09, 0.31]	0.00
Modus of delivery (CS)			
	Factor OR 95% *CI p-value*		
C. placental abruption	38.81	[12.96, 116.19]	0.00
P. placental abruption	6.79	[2.25, 20.52]	0.001
Placenta previa	2325.60	[254.49, 21252.00]	0.00
Unknown etiology	9.99	[3.40, 29.33]	0.00
GA at delivery (weeks)	0.91	[0.89, 0.94]	0.00
Diabetes	7.24	[2.19, 23.92]	0.001
Previous miscarriage	7.23	[2.04, 25.59]	0.002
Smoking	5.24	[2.79, 9.83]	0.00

delivery, with all other factors unchanged, an average decrease of 0.51 in Apgar score at fifth minute is predicted. Other factors that are found to be significant for Apgar score at fifth minute, following late vaginal bleeding in pregnancy, are Apgar score at first minute (p-value = 0.00, β = 0.20, 95% CI [0.09, 0.31]) and cause of hemorrhage, in particular causes non related to pregnancy (p-value = 0.00, β = 0.31, 95% CI [0.13, 0.49]) and

[2]APH = antepartum hemorrhage, GA = gestational age, C. placental abruption = central placental abruption, P. placental abruption = peripheral placental abruption, Non-pregnancy = non pregnancy related causes.

unknown (p-value = 0.02, β = 0.16, 95% CI [0.02, 0.30]). Finally, according to our data, modus of delivery does not significantly alter Apgar score, not even at the first minute (p-value = 0.82).

Multiple logistic regression analysis was used to determine the factors that have a significant impact on the selection of modus of delivery: vaginal, assisted or not, versus CS (**Table 3**). As expected, pregnancies complicated with placenta previa (p-value = 0.00, OR = 2325.60, 95% CI [254.49, 21252.00]) and central placental abruption (p-value = 0.00, OR = 38.81, 95% CI [12.96, 116.19]) are far more likely to result in CS compared to pregnancies with late vaginal bleeding due to cervical dilation. Likewise, compared to the latter, pregnant women presenting with peripheral placental abruption (p-value = 0.001, OR = 6.79, 95% CI [2.25, 20.52]) or bleeding of unknown etiology (p-value = 0.00, OR = 9.99, 95% CI [3.40, 29.33]) are respectively 6.79 and 9.99 times on average more likely to have a CS. The other significant factors for the selection of modus of delivery are presence of diabetes (p-value = 0.001, OR = 7.24, 95% CI [2.19, 23.92]), previous miscarriage (p-value = 0.002, OR = 7.23, 95% CI [2.04, 25.59]) and smoking habit (p-value = 0.00, OR = 5.24, 95% CI [2.79, 9.83]). Diabetic pregnant women presenting with late APH are 7.2 times on average more likely to give birth by CS compared to non-diabetic, assuming the other factors fixed. The case is the same for women who have had a previous miscarriage compared to those who have not. GA at delivery (p-value = 0.00, OR = 0.91, 95% CI [0.89, 0.94]) is a significant prognostic factor, in the general sense that an increase of one week in GA at delivery has a 9.9% increase in odds of giving vaginal birth. Birth weight (p-value = 0.58), advanced maternal age (p-value = 0.53) and presence of preeclampsia (p-value = 0.078) were not found to be significant independent predictive factors for modus of delivery in pregnancies complicated with late APH.

4. Discussion

Late APH remains an issue of great importance because it is relatively frequent with potential adverse outcomes for the mother and the neonate. The high neonatal mortality and morbidity seen with APH is mostly due to its strong association with preterm delivery [3] [8] [9]. However, a series of studies have demonstrated that APH is an independent factor for adverse neonatal outcomes in very preterm, as well as late preterm neonates. Among these groups APH has been independently associated with increased neonatal mortality and morbidity, particularly severe respiratory disorders, increased admission rate to NICU and increased hospital stay [28]-[31]. Our study intended to present an overview of the different causes of APH in the third trimester of pregnancy in relation to the perinatal outcome.

Overall, 253 neonates (52.7%) were born prematurely at gestational age below 37th week. Furthermore, 37 pregnancies (7.7%) resulted in giving birth prior to 32 weeks of gestation. Preeclampsia, diabetes, thyroid disorder and smoking were all associated with decrease of GA at birth in pregnancies complicated with APH. The cause of hemorrhage was found to be an important independent predictive factor for GA at birth, birth weight, Apgar scores at first and fifth minute and for the selection of modus of delivery. The Apgar scores' significant difference between the various causes of late APH as reported in our study is very small, probably without any clinical significance. In multivariable analysis, Apgar score did not alter significantly in proportion to birth weight, the significance only appeared for birth weight below 1500 gr, and in those cases Apgar score at first minute is predicted to be on average 1.04 smaller (with all the other factors fixed). Moreover, our data do not support a significant correlation between Apgar score at first minute and GA at birth in pregnancies complicated with late APH. This might be due to lack of power in very preterm infants as we have had 12 cases (2.5%) with GA at delivery smaller than 30 weeks. We might as well draw the conclusion that as long as infant birth weight is over 1500 gr, an increase in gestational age at birth (with expectant management) does not significantly improve Apgar score at first minute. However, GA at delivery is an important independent predictive factor for Apgar score at fifth minute, especially GA below 32 weeks. In accordance with our results, in a recent study GA at birth was associated with Apgar score at fifth minute for late preterm pregnancies with placenta previa [23]. Indeed, a number of recent studies would advocate the benefits of expectant management, even for late preterm neonates [23] [28] [30] [31]. Nevertheless, after 32th week of gestation the neonatal prognosis is good [32]. CS rate has been reported to be significantly higher with APH [11]. Our study did not recognize a pattern for the management of preterm or low birth weight infants in terms of modus of delivery in pregnancies complicated with late APH. Modus of delivery did not significantly alter Apgar score, not even at the first minute. Likewise, in a number of studies for very low birthweight infants no neonatal benefit in mortality or morbidity that supports CS versus vaginal delivery has been found in the absence of obstetrical indications [33] [34].

There are several limitations in this study. First, it is retrospective in design and this may have limited our ability to identify all the cofounders. Second, it included only singleton pregnancies and after spontaneous conception. Third, we do not report on the neonatal outcome after the fifth minute of life. Fourth, there is substantial heterogeneity among cases of late APH. However, we present an original article that addresses APH in the third trimester of pregnancy as it is actually encountered in every-day practice, with diverse causes, management and outcomes. Late APH remains an issue of great importance due to its frequency and potential adverse outcomes for the mother and the neonate. Though it is well studied, many questions remain still to be answered including the optimal timing of delivery, the timing and use of corticosteroids and the benefits of tocolysis with bleeding for women with late APH. These should ideally be addressed through prospective randomised studies.

5. Conclusion

APH in the third trimester of pregnancy requires immediate evaluation of the general condition of the pregnant woman and the fetus so as to achieve the best treatment. The cause of the hemorrhage is important in the prognosis of the neonatal outcome. As long as maternal and fetal status are ensured, expectant management, instead of emergency CS, seems to be more beneficial even for late preterm neonates.

Declaration of Interest

The authors report no declaration of interest.

References

[1] Chamberlain, G. and Morgan, M. (2002) ABC of Antenatal Care. *Consultant*, **302**, 1526-1530.

[2] Sakornbut, E., Leeman, L. and Fontaine, P. (2007) Late Pregnancy Bleeding. *American Family Physician*, **75**, 1199-1206.

[3] Ananth, C.V., Berkowitz, G.S., Savitz, D.A. and Lapinski, R.H. (1999) Placental Abruption and Adverse Perinatal Outcomes. *JAMA*, **282**, 1646-1651. http://dx.doi.org/10.1001/jama.282.17.1646

[4] Oyelese, Y. and Ananth, C.V. (2006) Placental Abruption. *Obstetrics & Gynecology*, **108**, 1005-1016. http://dx.doi.org/10.1097/01.AOG.0000239439.04364.9a

[5] Atkinson, A.L., Santolaya-Forgas, J., Blitzer, D.N., Santolaya, J.L., Matta, P., Canterino, J. and Oyelese, Y. (2014) Risk Factors for Perinatal Mortality in Patients Admitted to the Hospital with the Diagnosis of Placental Abruption. *The Journal of Maternal-Fetal & Neonatal Medicine*, **28**, 594-597.

[6] Faiz, A.S. and Ananth, C.V. (2009) Etiology and Risk Factors for Placenta Previa: An Overview and Meta-Analysis of Observational Studies. *The Journal of Maternal-Fetal & Neonatal Medicine*, **13**, 175-190.

[7] Royal College of Obstetricians and Gynaecologists (2011) Placenta Praevia, Placenta Praevia Accreta and Vasa Praevia: Diagnosis and Management. RCOG, London, 27.

[8] Vahanian, S.A., Lavery, J.A., Ananth, C.V. and Vintzileos, A. (2015) Placental Implantation Abnormalities and Risk of Preterm Delivery: A Systematic Review and Metaanalysis. *American Journal of Obstetrics & Gynecology*, **213**, S78-S90. http://dx.doi.org/10.1016/j.ajog.2015.05.058

[9] Bhandari, S., Raja, E., Shetty, A. and Bhattacharya, S. (2014) Maternal and Perinatal Consequences of Antepartum Haemorrhage of Unknown Origin. *BJOG*: *An International Journal of Obstetrics & Gynaecology*, **121**, 44-52. http://dx.doi.org/10.1111/1471-0528.12464

[10] Van Altvorst, M.E.W.A., Chan, E.H.Y., Taylor, R.S., Kenny, L.C., Myers, J.E., Dekker, G.A., North, R.A. and McCowan, L.M.E. (2012) Antepartum Haemorrhage of Unknown Origin and Maternal Cigarette Smoking beyond the First Trimester. *Australian and New Zealand Journal of Obstetrics and Gynaecology*, **52**, 161-166. http://dx.doi.org/10.1111/j.1479-828X.2011.01398.x

[11] Chan, C.C. and To, W.W. (1999) Antepartum Hemorrhage of Unknown Origin—What Is Its Clinical Significance? *Acta Obstetricia et Gynecologica Scandinavica*, **78**, 186-190. http://dx.doi.org/10.1080/j.1600-0412.1999.780303.x

[12] McCormack, R., Doherty, D., Magann, E.F., Hutchinson, M. and Newnham, J.P. (2008) Antepartum Bleeding of Unknown Origin in the Second Half of Pregnancy and Pregnancy Outcomes. *BJOG*, **115**, 1451-1457. http://dx.doi.org/10.1111/j.1471-0528.2008.01856.x

[13] Leung, T.Y., Chan, L.W., Tam, W.H., Leung, T.N. and Lau, T.K. (2001) Risk and Prediction of Preterm Delivery in Pregnancies Complicated by Antepartum Hemorrhage of Unknown Origin before 34 Weeks. *Gynecologic and Obstet-*

ric Investigation, **52**, 227-231. http://dx.doi.org/10.1159/000052980

[14] Bener, N., Saleh, M. and Yousafzai, M.T. (2012) Prevalence and Associated Risk Factors of Antepartum Hemorrhage among Arab Women in an Economically Fast Growing Society. *Nigerian Journal of Clinical Practice*, **15**, 185-189. http://dx.doi.org/10.4103/1119-3077.97315

[15] Sinha, P. and Kuruba, N. (2009) Ante-Partum Haemorrhage: An Update. *Journal of Obstetrics and Gynaecology* (*Lahore*), **28**, 377-381.

[16] Giordano, R., Cacciatore, A., Cignini, P., Vigna, R. and Romano, M. (2010) Antepartum Haemorrhage. *Journal of Prenatal Medicine*, **4**, 12-16.

[17] Mukherjee, S., Bawa, A.K., Sharma, S., Nandanwar, Y.S. and Gadam, M. (2014) Retrospective Study of Risk Factors and Maternal and Fetal Outcome in Patients with Abruptio Placentae. *Journal of Natural Science, Biology and Medicine*, **5**, 425-428. http://dx.doi.org/10.4103/0976-9668.136217

[18] Boisramé, T., Sananès, N., Fritz, G., Boudier, E., Aissi, G., Favre, R. and Langer, B. (2014) Placental Abruption: Risk Factors, Management and Maternal-Fetal Prognosis. Cohort Study over 10 Years. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, **179**, 100-104. http://dx.doi.org/10.1016/j.ejogrb.2014.05.026

[19] Kobayashi, A., Minami, S., Tanizaki, Y., Shiro, M., Yamamoto, M., Yagi, S., Okutani, T., Kumagai, T., Higuchi, R. and Ino, K. (2014) Adverse Perinatal and Neonatal Outcomes in Patients with Chronic Abruption-Oligohydramnios Sequence. *Journal of Obstetrics and Gynaecology Research*, **40**, 1618-1624. http://dx.doi.org/10.1111/jog.12395

[20] Furukawa, S., Doi, K., Furuta, K. and Sameshima, H. (2014) The Effect of Placental Abruption on the Outcome of Extremely Premature Infants. *The Journal of Maternal-Fetal & Neonatal Medicine*, **28**, 705-708.

[21] Mastrolia, S.A., Baumfeld, Y., Loverro, G., Yohai, D., Hershkovitz, R. and Weintraub, A.Y. (2016) Placenta Previa Associated with Severe Bleeding Leading to Hospitalization and Delivery: A Retrospective Population-Based Cohort Study. *Journal of Maternal-Fetal and Neonatal Medicine*, 1-5. http://dx.doi.org/10.3109/14767058.2015.1131264

[22] Lal, A.K. and Hibbard, J.U. (2015) Placenta Previa: An Outcomes Based Cohort Study in a Contemporary Obstetrics Population. *Archives of Gynecology and Obstetrics*, **206**, S57. http://dx.doi.org/10.1007/s00404-015-3628-y

[23] Balayla, J., Wo, B.L. and Bédard, M.-J. (2015) A Late-Preterm, Early-Term Stratified Analysis of Neonatal Outcomes by Gestational Age in Placenta Previa: Defining the Optimal Timing for Delivery. *Journal of Maternal-Fetal and Neonatal Medicine*, **28**, 1756-1761. http://dx.doi.org/10.3109/14767058.2014.970529

[24] Furuta, K., Tokunaga, S., Furukawa, S. and Sameshima, H. (2014) Acute and Massive Bleeding from Placenta Previa and Infants' Brain Damage. *Early Human Development*, **90**, 455-458. http://dx.doi.org/10.1016/j.earlhumdev.2014.06.002

[25] Vergani, P., Ornaghi, S., Pozzi, I., Beretta, P., Russo, F.M., Follesa, I. and Ghidini, A. (2009) Placenta Previa: Distance to Internal os and Mode of Delivery. *American Journal of Obstetrics & Gynecology*, **201**, 266.e1–266.e5. http://dx.doi.org/10.1016/j.ajog.2009.06.009

[26] Fishman, S., Maheshwari, B. and Chasen, S. (2009) Antepartum Bleeding in Women with Placenta Previa. *American Journal of Obstetrics and Gynecology*, **40**, 39-42.

[27] Naz, F., Shakoor, U. and Sharaf, S. (2010) Comparison of Pregnancy Outcome in Placenta Previa versus Placenta Abruption. *Pakistan Journal of Medical and Health Sciences*, **4**, 149-152.

[28] Corchia, C., Ferrante, P., Da Frè, M., Di Lallo, D., Gagliardi, L., Carnielli, V., Miniaci, S., Piga, S., Macagno, F. and Cuttini, M. (2013) Cause-Specific Mortality of Very Preterm Infants and Antenatal Events. *Journal of Pediatrics*, **162**, 1125-1132. http://dx.doi.org/10.1016/j.jpeds.2012.11.093

[29] Gouyon, J.-B., Vintejoux, A., Sagot, P., Burguet, A., Quantin, C. and Ferdynus, C. (2010) Neonatal Outcome Associated with Singleton Birth at 34-41 Weeks of Gestation. *International Journal of Epidemiology*, **39**, 769-776. http://dx.doi.org/10.1093/ije/dyq037

[30] Phaloprakarn, C., Manusirivithaya, S. and Boonyarittipong, P. (2015) Risk Score Comprising Maternal and Obstetric Factors to Identify Late Preterm Infants at Risk for Neonatal Intensive Care Unit Admission *Journal of Obstetrics and Gynaecology Research*, **41**, 680-688. http://dx.doi.org/10.1111/jog.12610

[31] Scheuchenegger, A., Lechner, E., Wiesinger-Eidenberger, G., Weissensteiner, M., Wagner, O., Schimetta, W. and Resch, B. (2014) Short-Term Morbidities in Moderate and Late Preterm Infants. *Klinische Pädiatrie*, **226**, 216-220.

[32] A. P, G. F, and the EPIPAGE-2 Writing Group (2015) Survival and Morbidity of Preterm Children Born at 22 through 34 Weeks' Gestation in France in 2011: Results of the Epipage-2 Cohort Study. *JAMA Pediatrics*, **169**, 230-238. http://dx.doi.org/10.1001/jamapediatrics.2014.3351

[33] Barzilay, E., Gadot, Y. and Koren, G. (2016) Safety of Vaginal Delivery in Very Low Birthweight Vertex Singletons: A Meta-Analysis. *Journal of Maternal-Fetal and Neonatal Medicine*, 1-19. http://dx.doi.org/10.3109/14767058.2016.1141889

[34] Durie, D.E., Sciscione, A.C., Hoffman, M.K., Mackley, A.B. and Paul, D.A. (2011) Mode of Delivery and Outcomes in Very Low-Birth-Weight Infants in the Vertex Presentation. *American Journal of Perinatology*, **28**, 195-200. http://dx.doi.org/10.1055/s-0030-1266156