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Original Research

Perinatal outcomes of second trimester antenatal genital bleeding

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Summary

Objective: To evaluate the prognosis of singleton pregnancies complicated by genital bleeding during the 2nd trimester and to identify the factors associated with poor perinatal outcome. *Materials and Methods:* We conducted a retrospective study (January 2009 to December 2012), which included all women presenting with midtrimester bleeding (15 to 27 weeks of gestation). The cases were compared with women without bleeding, who delivered in our center during the same period. *Results:* Ninety-seven women were included (0.57% of the overall singleton births). An underlying placental cause was discovered by ultrasound in 56% of the cases (low-lying placenta, partially detached placenta or a combination of both of these pathologies). We report a significantly increased rate of preterm birth (47.4% *vs.* 12.2%; RR=3.9), perinatal mortality (11.3% *vs.* 1.3%; RR=8.8), PPROM (16.5% *vs.* 3.7%; RR=4.5; CI 95% [2.8-7.1]), and cesarean section (42.3% *vs.* 21%; RR=2; CI 95% [1.6-2.5]) in the bleeding group. The factors associated with preterm birth were recurrent bleeding (OR=4.7), gestational age > 22 WG at the first bleeding (OR=3.7), and low-lying placenta. *Conclusion:* Despite a low incidence, the occurrence of bleeding in the 2nd trimester of pregnancy should alert the physician because of increased perinatal morbi-mortality. These patients may thus require increased monitoring.

Key words: Vaginal bleeding; Ultrasound; Second trimester of pregnancy; Adverse pregnancy outcomes; Preterm delivery.

Introduction

Obstetrical hemorrhages are predictive of high morbidity rates and fetomaternal mortality. While uterine bleeding in the 1st and 3rd trimesters of pregnancy has been widely studied [1-4], bleeding occurring in the 2nd trimester has rarely been examined [5-7]. Thus, we thought it was important to describe the obstetrical and perinatal outcomes of this complication in order to better inform patients and to adapt the type of management. The objectives of this paper were to evaluate the prognosis of singleton pregnancies complicated by a uterine hemorrhage during the 2nd trimester and to identify the factors associated with poor perinatal outcome.

Materials and Methods

We conducted a single-center retrospective and descriptive study at the University Hospital Center of Toulouse; tertiary care center located in the South-West France, performing approximately 4,500 deliveries annually. In this study, we included singleton pregnancies complicated by at least one episode of genital hemorrhage during the 2nd trimester, between 15 and 27+6 weeks of gestation (WG), requiring a visit at the emergency room of the maternity section, between January 2009 and December 2012.

Women in labor or with premature rupture of membranes (PROM) at the time of admission and those with bleeding related to an obvious cervical lesion (ectropion, cervical changes) were excluded. We also excluded women eligible for a termination of pregnancy. The results were compared to those of all women having delivered > 22 WG in our hospital during the same period and who had not presented with bleeding (control group).

A complete obstetrical examination and transvaginal ultrasound were systematically performed upon admission. Three criteria were recorded for the characterization of hemorrhages: the date of onset in pregnancy, recurrence, and abundance. Hemorrhage was defined as severe if the bleeding had a hemodynamic impact or if blood transfusion was necessary, low when blood loss was minimal (less than the usual abundance of menstruation) and moderate in the remaining cases. Finally, five categories of ultrasound etiological diagnosis were established: low-lying placenta (LLP), partially detached placenta, a combination of partially detached placenta and LLP, placental abruption, and indeterminate. Women with LLP were classified into four types: lateral (type I), marginal (type II), partially (type III) or completely (type IV) covering the internal opening to the cervix. The diagnosis of partially detached placenta was made when the presence of a decidual hematoma without chorionic placental insertion abnormality could be identified via ultrasound without pelvic pain. Genital bleeding was considered to be of unknown etiology when the ultrasound scan was considered normal.

The obstetric outcome parameters studied were: gestational age at delivery, mode of delivery, and occurrence of preterm PROM (PROM < 37 WG). Perinatal outcome was studied as a function of the following parameters: condition of the child at birth (live or dead fetus), early neonatal death (< 7 day), preterm birth (PTB) rate (defined as the ratio between the number of PTB (<37 WG) and the total number of live births), and perinatal mortality (defined as stillbirths plus early neonatal mortality).

Data were recorded manually from the clinical records of patients identified from the maternity database. This study has been approved by the ethics committee for obstetric and gynecologi-

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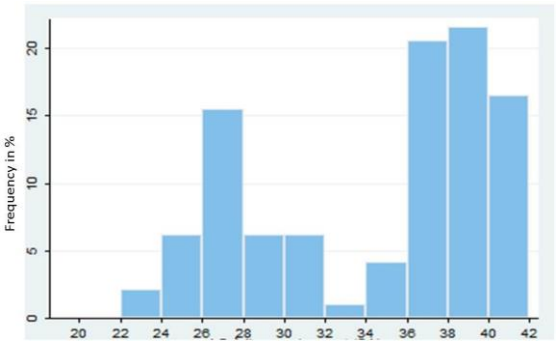

Figure 1. — Bimodal distribution of the gestational age at time of delivery.

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Statistical analysis: The description of variables combines the mean and standard deviation for those variables whose distribution approximated a normal distribution and the median and first and third quartiles in all other cases. For univariate analysis, comparison of the categorical variables in relation to the reference population was performed using Fisher's exact test in a bilateral formulation. Multivariate analysis was conducted to identify the factors associated with the different elements of obstetrical prognosis (prematurity, mortality, premature rupture of membranes, mode of delivery). This analysis used a reverse stepwise logistic regression that retained all variables emerging from the univariate analysis with a significance threshold of $p < 0.20$ as initially input in the regression model. The level of significance was set at $p = 0.05$ for all analyses. All statistical analyses were performed using the statistical software package STATA: Release 13.

Results

During the study period (four years), 17,890 births ≥ 22 WG occurred in our center, of which 17,009 were singleton births (95.1% of all births). Among these patients, 97 were included in the study for uterine hemorrhage in the 2nd trimester, representing 0.57% of singleton deliveries. The control group was made up of 16,912 of the remaining patients. Gestational age at delivery had a bimodal frequency distribution with two peaks, at 27 and 38 weeks (Figure 1).

Bleeding during the 1st trimester occurred in 24% of cases, and 24% of the women who delivered > 28 WG presented with recurrent bleeding during the 3rd trimester. One patient in two presented with one or more other episodes of bleeding.

The average age of the women who experienced bleeding in the 2nd trimester was 31.7 ± 5.7 years and the median parity was 1 (inter-quartile range [0-1]). Among the women presenting with bleeding, 9% had a history of PTB or late miscarriage and 3% were under treatment with potential risk of bleeding at the time of the episode (preventive treatment with heparin or anti-platelet). No pathology of hemostasis had been reported. A recent predisposing cause (< 7 days before the onset of bleeding) was found in five women, which included the following: one patient who experienced a car crash on the same day, two patients who had sex on the same day, and two patients who had bled at 24 and 26 WG and had undergone cervical cerclage at 13 and 14 WG, respectively.

The abundance of bleeding was classified as moderate in 67% of cases. Approximately half of the patients (53%) had been hospitalized for observation after their arrival to the emergency room (stay length: 1-77 days, but < 9 days in half of the cases). A single period of hospitalization occurred in 66% of the cases. The initial ultrasound examination identified a placental etiology in 56% of the cases: LLP 33%, partially detached placenta 12%, and a combination of partially detached placenta and LLP 11%. The LLP cases were further subcategorized as follows: 35% type I, 19% type II, 5% type III, and 42% type IV. No abruptio placentae were observed during the study duration. In 44% of cases, no etiology was found. The "bleeding group" was associated with poor obstetrical outcomes compared with the control group. The main results are reported in Table 1.

Three cases of early neonatal death (before day 7) were observed: two PTB at 26+4 and 27+2 WG. respectively, and a death following surgical intervention for a diaphragmatic hernia performed two days after a C-section at 38 WG. Three cases of stillbirth were reported < 26 WG, and

Table 1. — *Main obstetrical and perinatal complications associated with the occurrence of a hemorrhage during the 2nd trimester of pregnancy (univariate analysis).*

	Bleeding during 2nd trimester (*N=97*)	**Control group (*N=16,912*)**	**RR [CI 95%]**	***p***
	Number of cases (%)			
Preterm birth	46 (47.4)	2061 (12.2)	3.9 [3.1 – 4.8]	*<0.0001*
Preterm <32 WG	36 (37.1)	908 (5.3)	6.9 [5.3 – 9]	*<0.0001*
PPROM	16 (16.5)	622 (3.7)	4.5 [2.8 – 7.1]	*<0.0001*
Cesarean section	41 (42.3)	3554 (21)	2.0 [1.6 – 2.5]	*<0.0001*
Perinatal mortality	11 (11.3)	218 (1.3)	8.8 [5 – 15.6]	*<0.0001*
Intrauterine mortality	8 (8.2)	130 (0.8)	10.7 [5.4 - 21.3]	*<0.0001*
Early neonatal mortality	3 (3.1)	88 (0.5)	5.9 [1.9 – 18.5]	*0.015*

CI: confidence interval; PPROM : preterm premature rupture of membranes; RR : Relative risk; WG : weeks of gestation.

Table 2. — *Risk of preterm birth associated with hemorrhages during the 2nd trimester of pregnancy according to the presumed origin of bleeding and associated factors.*

			All preterm births		**Severe prematurity (28 to 32 WG)**		**Extreme prematurity (22 to 27 WG)**	
			%	*p*	*%*	*p*	*%*	*p*
Clinical Characteristics	Abundance of bleeding	Moderate to heavy	52.4	0.11	42.9	0.039	28.6	0.053
		Light	34.5		20.6		10.3	
	Gestational age at first episode	>22 WG	58.8	0.018	51	0.003	35.3	0.005
		<22 WG	34.8		21.7		10.9	
	Recurrence of bleeding	Yes	60.4	0.014	47.9	0.035	27.1	0.47
		No	35.4		27.1		20.8	
	Number of episodes	More than 3	64.7	0.012	52.9	0.018	26.5	0.64
		1 or 2	38.1		28.6		22.2	
Ultrasound Diagnosis	Partially detached placenta	Yes	66.7	0.15	58.3	0.12	25	1
		No	44.7		34.1		23.5	
	Low-lying placenta	Yes	37.5	0.17	21.9	0.029	12.5	0.069
		No	52.3		44.6		29.2	
	Partially detached and low-lying placenta	Yes	63.6	0.25	54.5	0.32	36.7	0.28
		No	45.3		34.9		22.1	
	All placental causes	Yes	49.1	0.71	36.3	0.86	20	0.33
		No	45.2		38.1		28.6	
	Characterization of low-lying placenta	III or IV	50	0.47	25	0.49	15	0.7
		I or II	39.1		34.8		21.7	

WG : weeks of gestation.

Table 3. — *Risk of preterm premature rupture of membranes associated with hemorrhages during the 2nd trimester of pregnancy according to the presumed origin of the bleeding and associated factors.*

			Preterm premature rupture of membranes	
			%	*p*
Clinical Characteristics	Abundance of bleeding	Moderate to heavy	16.9	1
		Light	17.2	
	Gestational age at first episode	> 22 WG	20	0.44
		< 22 WG	14	
	Recurrence of bleeding	Yes	21.7	0.27
		No	13	
	Number of episodes	More than 3	25	0.15
		1 or 2	13.1	
Ultrasound Diagnosis	Partially detached placenta	Yes	50	0.005
		No	12.3	
	Low-lying placenta	Yes	0	0.002
		No	25.4	
	Partially detached and low-lying placenta	Yes	10	1
		No	18.1	
	All placental causes	Yes	13.5	0.28
		No	22	
	Characterization of low-lying placenta	III or IV	0	1
		I or II	4.5 %	

WG: weeks of gestation.

three cases of intrauterine fetal death (IUFD) were reported > 26 weeks: chorioamnionitis at 30 WG (confirmed by a pathological examination of the placenta), severe growth retardation of placental origin associated with preeclampsia at 29+3 WG, and IUFD at 26+4 WG of indeterminate origin.

In the univariate analysis, gestational age ≥ 22 WG at the first episode and the presence of at least one recurrence of bleeding were significant determinants associated with PTB: 58.8% for gestational age ≥ 22 WG at the first episode *vs.* 34.8% < 22 WG ($p = 0.018$) and 60.4% for bleeding with recurrence *vs.* 35.4% for an isolated episode ($p = 0.014$). In contrast, no link was demonstrated between the abundance of bleeding or its causes and prematurity (Table 2).

Two ultrasound abnormalities were significantly associated with the risk of PPROM: partially detached placenta (50% *vs.* 12.3%, $p = 0.005$) as an aggravating factor and LLP (0% *vs.* 25.4% $p = 0.002$) as a protective factor (Table 3). No significant association was demonstrated between PPROM and abundance of bleeding, their recurrence or the time of occurrence.

The sole significant determinant associated with the rate of C-section was the recurrence of bleeding (52.1% *vs.* 31.2% for a single episode, $p = 0.038$). No determinant was significantly associated with perinatal mortality (Table 4). In the multivariate analysis, three determinants were significantly and independently associated with the risk of prematurity: gestational age at the time of the first episode of bleeding, recurrence of bleeding, and LLP found on ultrasound (Table 5).

The risk of PPROM and LLP were not included in the multivariate analysis because having LLP negated the risk of PPROM in our study. Only partially detached placenta was significantly and independently associated with the risk of PPROM (OR=7.1; $p = 0.001$). The only factor significantly associated with the risk of cesarean delivery in the multivariate analysis was the recurrence of bleeding

Table 4. — *Perinatal mortality, intrauterine fetal death, and early neonatal mortality resulting from hemorrhage during the 2nd trimester of pregnancy according to the presumed origin of the bleeding and associated factors.*

			Perinatal mortality		Intrauterine fetal death		Early neonatal mortality	
			%	*p*	%	*p*	%	*p*
Clinical Characteristics	Abundance of bleeding	Moderate to heavy	9.5	0.72	7.9	0.70	1.6	0.53
		Light	13.8		10.3		3.4	
	Gestational age at first episode	>22 WG	7.8	0.25	5.9	0.47	2	0.60
		<22 WG	15.2		10.9		4.3	
	Recurrence of bleeding	Yes	12.5	0.75	10.4	0.71	2.1	1
		No	10.4		6.3		3.2	
	Number of episodes	More than 3	14.7	0.51	11.8	0.45	2.9	1
		1 or 2	9.5		6.3		3.2	
Ultrasound Diagnosis	Partially detached placenta	Yes	50	0.005	16.7	0.28	0	1
		No	12.3		7.1		3.5	
	Low-lying placenta	Yes	0	0.002	9.4	1	0	0.55
		No	25.4		7.7		4.6	
	Partially detached and low-lying placenta	Yes	9.1	1	9.1	1	0	1
		No	11.6		8.1		3.5	
	All placental causes	Yes	10.9	1	10.9	0.46	0	0.078
		No	11.9		4.8		7.1	
	Characterization of low-lying placenta	III or IV	10	1	10	1	0	-
		I or II	8.7		8.7		0	

WG: weeks of gestation.

Table 5. — *Factors associated with prematurity, preterm premature rupture of the membranes, and cesarean section (multivariate analysis)*

	Odds ratio	95% CI	*p* value
Prematurity			
Gestational age at the 1st episode	3.7	1.4 – 9.5	0.007
Recurrence of bleeding	4.7	1.8 – 12.6	0.002
Low-lying placenta	0.4	0.1 – 1	0.047
Preterm premature rupture of membranes			
Partially detached placenta	7.1	2 – 25.4	0.001
Cesarean section			
Recurrence of bleeding	2.4	1.0 – 5.5	0.04

CI : confidence interval.

(OR=2.4; $p = 0.04$).

Discussion

The present study revealed a significant association between bleeding during the 2nd trimester and adverse pregnancy outcomes: PTB (RR=3.9), C-section (RR=2), PPROM (RR=4.5), and perinatal mortality (RR=8.8). Recurrence of bleeding, gestational age at first episode, LLP, and partially detached placenta were factors significantly and independently associated with poor perinatal outcomes.

The incidence of bleeding during the 2nd trimester observed in our study (0.57% of singleton deliveries) is identical to that found in a previous study conducted in our center [5], but lower than that reported by other: 9.2% Ramaecker *et al.* [8] (cohort study 2,988 women), 5.5% Yang *et al.* [6] (cohort study 2,829 women), and 2.6% Hossain *et al.* [9] (cohort study 2,678 women). This lower incidence may be explained by the strict selection criteria at inclusion (exclusion of cases with bleeding of cervical origin, PPROM, multiple pregnancies), and due to uncertainties in the completeness of data for pregnancies that were terminated prematurely before 22 WG.

The etiology of bleeding during the 2nd trimester has not been studied well. Koifman *et al.* [10] reported in 2008 on a retrospective cohort study of 1,580 women and found rates of 63.5% for abruption and 36.5% for placenta previa. This paper does not mention any bleeding of undetermined origin. In agreement with these data our study showed a majority of placental causes. However, ultrasound scanning was considered normal in 44% of the cases. In the present study, the diagnosis of partially detached placenta was considered only if the hematoma was apparent at ultrasound scan. It is likely, and generally accepted, that some unexplained bleeding may actually have corresponded to marginally and partially detached placentas that were not detected by an ultrasound scan.

The risk of PTB observed in our study (RR=3.9 [3.1-4.8] *vs.* control) is consistent with our previous findings (34.5% preterm birth) [5], with data previously reported by Ramaecker *et al.* [8] (RR=1.56, 95% CI [1.14-2.14]) and with the meta-analysis of Ananth *et al.* [11], which examined the outcomes of pregnancies complicated by bleeding (RR for PTB=2.2, 95% CI [2.1-2.4]). The recurrence of bleeding was associated with an increased rate of PTB in our series in agreement with the results reported by Yang and Jouppila (RR=1.7, 95% CI [1.2-2.3]) [6, 12].

We found no link between the amount of bleeding and the risk of PTB (RR=1.5, 95% CI [0.9-2.6]) in accordance

with Harlev (RR=1.5, 95% CI [1.0-2.2]) [13]. However, published results considering the amount of bleeding are conflicting. In a retrospective study of 128 women who had bleeding between 16 and 24 WG, Towers *et al.* [7] showed that bleeding considered minimal, regardless of placental location, was associated with favorable pregnancy outcomes in 87% of cases, whereas heavy bleeding without placenta praevia was associated with poor perinatal outcomes (50% fetal loss, 82% PTB, 8% neonatal deaths before discharge from the hospital). The outcome was better when excessive bleeding was related to placenta praevia, which can be explained by the fact that bleeding with a normally inserted placenta is more likely to be the result of an abruption.

The criterion of the abundance of bleeding is difficult to quantify reproducibly and almost impossible to appreciate in retrospective studies. A semi-quantitative observational scale would help to improve the assessment of the volume of blood loss.

The present study did not show any difference according to the results of the initial ultrasound scan. The small size is probably one of the reasons. In our previous study [5], perinatal outcome was favorable (no different from the control group) when the origin of bleeding was unknown and ultrasonographic examination was considered normal compared with placental abnormalities.

Other studies have found conflicting results, showing a significant association between idiopathic vaginal bleeding during the 2nd half of pregnancy and PTB (OR=4.31, 95% CI [3.84-4.84]) or PPROM (OR=3.4, 95% CI [1.8-6.2]) [13, 14]. In a recent study, Bhandari *et al.* [15] showed that pregnancies complicated by antepartum bleeding of unknown origin are at greater risk of PTB (aOR=1.23, 95% CI [1.16-1.31]) and induced labour (aOR=2.30, 95% CI [2.11-2.50]).

Most studies found an increased risk of PPROM in cases of bleeding in the 1st and/or 2nd trimester (OR=3.29, 95% CI [1.31-8.24] [4] and RR=1.7, 95% CI [1.0-2.9] [6]). The presence of a partially detached placenta at the chorionic-decidual interface may induce coagulation cascade, with increased thrombin and plasmin, which ultimately activates matrix metalloproteinases (MMPs) at the onset of the degradation of the collagens in the fetal membranes. This local reaction is considered as a factor weakening the membranes [16]. Conversely, in our study, the ultrasound evidence showed that low-lying placenta appears to protect against the risk of PPROM (OR=0, 95% CI: [0-0.4], p = 0.002), which has not been demonstrated in previous studies.

We showed an increased C-section rate (42% in the bleeding group *vs.* 21% in the control group), which is consistent with other published data (72.9% *vs.* 12.1%) [10]. The frequency of placental abnormalities (insertion anomalies, detachment) probably explains the high caesarean rate.

Perinatal mortality was increased in our population, in agreement with the findings of Koifman *et al.* [10]. This author showed, in a cohort study of 1,580 women who bled in the 2nd half of pregnancy, an increased perinatal mortality (14% *vs.* 1.1%; OR=15.5 [13.6-17.6]) and significantly decreased APGAR scores. In our previous study with the same inclusion criteria, we observed a perinatal mortality rate of 17% [5], which is no different from the rate found in the current study. Progress in the improvement of perinatal care (close monitoring, antenatal corticosteroid therapy, and neonatal resuscitation) has not translated to improvements in the epidemiological data.

Our study included biases due mainly to its retrospective nature. Quantification of the amount of bleeding was not very accurate because there is as yet no validated scale to measure such data. However, our inclusion criteria were stricter than those used in previous studies, allowing for a more selective analysis of this symptom. The ability to compare our results with a similar study conducted ten years ago in the same hospital is one of the strong points of this study.

Despite its low incidence, the occurrence of mid-trimester bleeding should alert the physician because of the increased risk of prematurity and perinatal mortality. We have highlighted two additional important factors: the recurrence and the late onset of bleeding (>22 WG). Partially detached placenta is a cause of the abrupt onset of bleeding in the context of uterine hyperactivity, even when the initial ultrasound appears normal. These patients should be considered at high risk of PTB and will require increased monitoring and/or antenatal steroids. Further complementary studies could be useful to clarify associated factors.

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