Analysis of 339 pregnancies in 181 women with 13 different forms of inherited thrombocytopenia

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ABSTRACT

Pregnancy in women with inherited thrombocytopenias is a major matter of concern as both the mothers and the newborns are potentially at risk of bleeding. However, medical management of this condition cannot be based on evidence because of the lack of consistent information in the literature. To advance knowledge on this matter, we performed a multicentric, retrospective study evaluating 339 pregnancies in 181 women with 13 different forms of inherited thrombocytopenia. Neither the degree of thrombocytopenia nor the severity of bleeding tendency worsened during pregnancy and the course of pregnancy did not differ from that of healthy subjects in terms of miscarriages, fetal bleeding and pre-term births. The degree of thrombocytopenia in the babies was similar to that in the mother. Only 7 of 156 affected newborns had delivery-related bleeding, but 2 of them died of cerebral hemorrhage. The frequency of delivery-related maternal bleeding ranged from 6.8% to 14.2% depending on the definition of abnormal blood loss, suggesting that the risk of abnormal blood loss was increased with respect to the general population. However, no mother died or had to undergo hysterectomy to arrest bleeding. The search for parameters predicting delivery-related bleeding in the mother suggested that hemorrhages requiring blood transfusion were more frequent in women with history of severe bleedings before pregnancy and with platelet count at delivery below 50 x 10^9/L.

Introduction

Partum-related hemorrhage is the leading cause of morbidity and mortality among pregnant women resulting in 140,000 deaths each year.[1] Although the majority of these deaths occur in low income countries, excessive bleeding at delivery is also frequent in high resource countries. In Australia, Canada and the US, 3-7% of deliveries in 2005 were complicated by primary postpartum hemorrhage.[2]

The bleeding risk is expected to be higher in women with inherited thrombocytopenias (ITs) because of low platelet counts and associated defects of platelet function in some disorders. Nevertheless, few studies have investigated this topic and there is little evidence to guide management of pregnancy and delivery.[3] Fetal and neonatal outcomes are also not well-described.

One of the forms of IT most investigated with respect to pregnancy is biallelic Bernard-Soulier Syndrome (bBSS), probably because of its early identification in the middle of the last century. A systematic review of the literature published in 2010 identified 16 relevant articles, all case reports, describing 30 deliveries in 18 bBSS women.[4] Excessive bleeding occurred in 18 cases of which blood transfusion was required in 15. All women survived, but 2 required emergency hysterectomy. Concerning the fetus, there was one intra-uterine death caused by gastrointestinal bleeding and one neonatal death due to

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antepartum intracranial hemorrhage. On this basis, it has been concluded that bBSS is associated with a very high risk of serious bleeding in the mother and the neonate.

Some information on pregnancy outcome is available also for *MYH9*-related disease (*MYH9*-RD), one of the most frequent forms of IT. A recent review of the literature examined 25 case reports and one case series describing a total of 75 pregnancies in 40 women.[5] Postpartum hemorrhage in the mother occurred in 4 cases, while no obvious bleeding complications were reported among the newborns. Based on these data, *MYH9*-RD does not seem to increase bleeding risk either in mothers or neonates.

Limited data on pregnancy outcomes have been provided for patients with mild to moderate thrombocytopenia due to monoallelic BSS (mBSS), in all cases induced by the p.Ala156Val substitution in GPIb alpha (Bolzano mutation).[6] Overall, 20 women delivered 34 children with no excessive maternal or neonatal bleeding. Although the authors did not provide information on management of pregnancies and childbirths, this study suggests that women with mBSS have gestational outcomes similar to healthy subjects.

A moderate risk of bleeding during delivery has been reported in a series of subjects with thrombocytopenia induced by *ANKRD26* mutations (*ANKRD26*-related thrombocytopenia, *ANKRD26*-RT).[7] Thirteen patients gave birth, either vaginally or by caesarean section, with bleeding complications in 3 women. No information was provided on prophylactic treatment or neonatal outcomes.

The paucity of evidence presently available, therefore, indicates that maternal and neonatal bleeding risk during pregnancy and delivery may vary with different forms of IT, ranging from very severe to very mild. However, the evidence concerns only four ITs and largely derives from case reports or series of patients not specifically investigated with respect to pregnancy.

To remedy this scarcity of information, we performed a retrospective, multicentric study aimed at systematically collecting and analyzing pregnancy outcomes in a large series of patients with well-defined forms of IT.

Methods

Patients

This study was promoted by the Scientific Working Group on Thrombocytopenias and Platelet Function Disorders of the European Hematology Association (EHA) and was announced at the 2013 EHA Congress in Stockholm. Clinical centers that, based on scientific publications and/or personal knowledge, represent points of reference for ITs were invited to participate. Forty-five institutions took part in the study. They were asked to analyze their databases and extract data on pregnancies in women with ITs. A series of questions had to be answered for each enrolled case related to the base-line characteristics of the mother, the course of pregnancy, and the management and outcome of delivery, with particular attention to the bleeding events in the mother and the newborn.

Only women with diagnoses confirmed by genetic analysis were eligible for the study. As an exception, positivity of the immunofluorescence test for *MYH9*-related disease (*MYH9*-RD) was considered sufficient for making the diagnosis in patients where mutational screening was not available because of its very high sensitivity and specificity.[8]

Neonates for whom genetic screening was not available were considered affected from the same illness as the mother whenever they were thrombocytopenic and the mother had a dominant disorder. In case of recessive disorders, documentation that the parents were carriers of the disease was required.

The Institutional Review Board of the IRCCS Policlinico San Matteo Foundation of Pavia, Italy, approved the study protocol. The study was performed in accordance with the Declaration of Helsinki, and each center complied with local ethical rules.

Classification of bleeding

Because of the retrospective nature of the study, it was not possible to use the most recent bleeding scores that are most suited to patients with primary hemostasis defects. Spontaneous bleeding tendency in the mother before pregnancy was, therefore measured by the World Health Organization bleeding scale: grade 0 indicates no bleeding; grade 1, petechiae; grade 2, mild blood loss; grade 3, gross blood loss; grade 4, debilitating blood loss.[9]

The amount of blood loss has been used by most authors to identify post-partum hemorrhages.[10] However, this parameter was available for only a few patients, and we could not use it. Therefore, we identified two definitions for excessive bleeding at delivery: "excessive bleedings requiring blood transfusion" (EBBT), based on transfusion of platelets and/or red blood cells during or after delivery to treat bleeding (prophylactic platelet transfusions prior to delivery were not considered for definition of EBBT), and "all excessive bleedings" (AEB), which includes not only patients receiving platelets and/or red blood cells, but also subjects who did not receive blood products and were judged by the treating physician as presenting larger than normal blood loss. Thus, EBBT is a narrow definition that is expected to identify the most serious blood loss, while AEB is a broader definition that also encompasses less severe bleedings.

The same criteria were used to define increased bleedings with previous surgery. Any type of bleeding in newborns was considered abnormal and recorded. Miscarriage was defined as spontaneous expulsion from the uterus of the products of conception before viability. Pre-term birth was defined as live birth of a neonate of less than 37 weeks gestational age. Platelet count was measured by cell counters available in each center.

Statistical analysis

Data were described as median and 25th-75th percentiles if continuous and as counts if categorical. EBBT and AEB incidence and 95% confidence intervals (95%CI) were computed. Generalized linear regression models were used to compare platelet counts between and within groups; Huber-White robust standard errors were calculated to account for intra-patient correlation. Logistic regression was used to assess the association of a series of patients' characteristics with bleeding; Odds Ratios (OR) and 95%CI were computed. ROC curve analysis was used to identify the optimal cut offs for the association of platelets counts and bleedings. Stata 13 (StataCorp, College Station, TX, USA) was used for computation. Two-sided $P<0.05$ was considered statistically significant.

Results

Not all data were available for all investigated patients, and results described below report the number of investigated cases for which data were available. In case the number of investigated patients is not reported, it is intended that all patients were studied.

Womens' base-line characteristics

One hundred and eighty-one women with 13 different forms of IT who had a total of 339 pregnancies were investigated retrospectively by 45 centers in 20 countries. In 169

women, diagnoses were confirmed by the identification of mutations in the candidate genes, while in 12 subjects a diagnosis of *MYH9*-RD was made on the basis of a positive immunofluorescence test for the distribution of *MYH9* protein in neutrophils.[8] Of note, 18 of 24 women with the diagnosis of mBSS had the p.Ala156Val substitution in GPIb alpha (Bolzano mutation).[6]

Patients' features before pregnancy are reported in Table 1. A feature common to many investigated patients was the difficulty of making a correct diagnosis of IT, as shown by the observation that 57 subjects were initially misdiagnosed with immune thrombocytopenia. Forty-four of these women received unnecessary treatment, including splenectomy in 15 cases. Difficulties in diagnosis is also demonstrated by the finding that the inherited origin of thrombocytopenia was recognized in adulthood in most cases, with a mean age at diagnosis of 30 years. These findings underscore the need to maintain a high index of suspicion for ITs in the evaluation of patients with thrombocytopenia.[11]

Thrombocytopenia was on average moderate, with a mean platelet count of 60 x 10^9/L in the whole case series and a mean platelet count higher than 45 x 10^9/L in all dis-

Table 1. Diagnosis and base-line features of investigated women with different forms of inherited thrombocytopenia who had one or more pregnancies.

Disorder (abb., phenotype MIM number)	N. of women	Median age in years at diagnosis, 25th-75th percentile	N. of patients with a previous diagnosis/ medical treatment/ splenectomy for immune thrombocytopenia	Median platelet count before pregnancy x10^9/L, 25th-75th percentile	WHO bleeding scale*, N. of patients with a history of spontaneous bleeding of grades 0-1-2-3-4	N. of patients receiving surgery	N. of patients receiving prophylactic platelet transfusions N. of evaluated patients	N. of patients with EBBT at surgery N. of evaluated patients	N. of patients with AEB at surgery N. of evaluated evaluated
MYH9-related disease (*MYH9-RD, 600208*)	98	31, 19-42	41/32/11	40, 23-64	39-21-30-5-3	67	26 (67)	9 (67)	20 (67)
ANKRD26-related thrombocytopenia (*ANKRD26-RT, 188000*)	23	21, 11-40	8/6/3	54, 30-84	6-4-7-3-3	12	2 (11)	0 (11)	1 (11)
Biallelic Bernard-Soulier syndrome (*bBSS, 231200*)	13	33, 26-36	3/3/1	50, 23-92	5-0-5-2-1	8	1 (7)	1 (7)	2 (7)
Monoallelic Bernard-Soulier syndrome (*mBSS, 231200*)	24	31, 19-41	1/1/0	86, 77-111	12-4-3-5-0	13	1 (13)	0 (13)	3 (13)
ACTN1-related thrombocytopenia (*ACTN1-RT, 615193*)	9	21, 17-40	0/0/0	77, 65-94	2-3-2-2-0	4	0 (4)	0 (4)	2 (4)
Familial platelet disorder and predisposition to acute myelogenous leukemia (*FPD/AML, 601399*)	4	37, 26-38	1/1/0	116, 93-138	0-0-3-0-1	2	0 (2)	0 (2)	1 (2)
ITGB3-related thrombocytopenia (*ITGB3-RT, 187800*)	3	16, 11-37	0/0/0	78, 65-114	1-0-0-2-0	3	3 (3)	0 (3)	0 (3)
Platelet-type von Willebrand disease (*VWDP, 177820*)	2	27, 27-28	1/0/0	80, 30-130	0-1-0-0-1	1	0 (1)	0 (1)	1 (1)
Gray platelet syndrome (*GPS, 139090*)	1	13	1/1/0	65	0-0-0-1-0	1	1 (1)	0 (1)	0 (1)
FLNA-related thrombocytopenia (*FLNA-RT, nd*)	1	23	0/0/0	43	1-0-0-0-0	1	0 (1)	0 (1)	0 (1)
TUBB1-related thrombocytopenia (*TUBB1-RT, 613112*)	1	4	1/0/0 0 (1)	100	0-1-0-0-0	1	0 (1)	0 (1)	
Velocardiofacial syndrome (*VCFS, 192430*)	1	34	0/0/0	75	0-1-0-0-0	1	0 (1)	0 (1)	0 (1)
CYCS-related thrombocytopenia (*CYCS-RT, 612004*)	1	25	0/0/0	35	0-1-0-0-0	1	0 (1)	0 (1)	0 (1)
Total	181	29 (19-39)	57/44/15	57 (30-82)	66-36-50-20-9	114	34 (112)	10 (112)	30 (112)

**World Health Organization bleeding scale: grade 0, no bleeding; grade 1, petechiae; grade 2, mild blood loss; grade 3, gross blood loss; grade 4, debilitating blood loss; EBBT: excessive bleeding requiring blood transfusion; AEB: all excessive bleedings; 25th-75th: 25th-75th percentiles.*

orders for which more than one patient was examined. However, severely reduced platelet counts were observed in a few cases. In this regard, it is important to note that platelet counts were measured by electronic cell counters and that these instruments are known not to recognize very large platelets.[12] It is, therefore, expected that the degree of thrombocytopenia was overestimated in patients with inherited macrothrombocytopenias, especially those with *MYH9*-RD and bBSS who typically have giant platelets.

Spontaneous bleeding tendency before pregnancy was on average mild. WHO grade 3 and 4 bleeding were reported in only 20 and 9 of 181 subjects, respectively.

Perioperative AEB and EBBT were reported in 30 and 10 of 112 women receiving surgery, respectively.

Gestations

No variation in severity of the pre-existing bleeding tendency was reported during pregnancy (*data not shown*).

The course of gestation was uneventful in 304 cases, while miscarriage was reported in 34 pregnancies (10.1%, 95%CI: 7.2-14.0). One therapeutic interruption of pregnancy because of fetal malformation was reported. The incidence of miscarriage is superimposable to that observed in a large population of white women in the US (10.2%).[13] Pregnancy loss occurred in the first trimester in 29 cases, in the second in 5 cases, and in the third in one case.

Pre-term birth was recorded for 30 pregnancies (9.9%, 95%CI: 6.8-13.7), and thus the frequency of this event was not significantly different from that observed in a general population of Western countries (7.4%).[14] All pre-term deliveries occurred at a gestational age of 36 or 37 weeks.

Newborns

Diagnostic definition was possible in 278 newborns: 156 were affected by ITs, while 122 were unaffected.

Comparison of platelet counts in the 126 affected newborns for which this information was available with baseline platelet counts in their mothers revealed that the degree of thrombocytopenia was similar, although the small observed difference was statistically significant (mean platelet count in the newborns 69 x 10^9 platelets/L, in the mothers 58 x 10^9/L; P=0.020).

Bleeding signs consisting of petechiae were observed in 5 affected neonates, while fatal cerebral hemorrhages were

Table 2. Characteristics of pregnancy, delivery and newborns in women with inherited thrombocytopenias. The number of investigated patients is reported (in brackets) in case of missing data.

Disorders	N. of pregnancies/ miscarriages	Median age in years at delivery, 25th-75th percentile	Median platelet count at delivery x10^9/L, 25th-75th percentile (N. of evaluated deliveries)	N. of term/ preterm deliveries (N. of evaluated deliveries)	N. of vaginal deliveries/ cesarean sections (N. of evaluated deliveries)	N. of deliveries with general/ spinal or epidural/no anesthesia (N. of evaluated deliveries)	N. of deliveries with prophylactic platelet transfusion (N. of evaluated deliveries)	N. of deliveries with EBBT, % incidence, CI (N. of evaluated deliveries)	N. of deliveries with AEB, % incidence, CI (N. of evaluated deliveries)	N. of healthy newborns affected by the mother disorder (N. of evaluated babies)	N. of affected newborns with bleedings (N. of evaluated babies)
MYH9-RD	185/21	28, 24-32	60, 34-80 (86)	142/20 (162)	94/69 (163)	54/34/73 (163)	31 (161)	13, 8.3, 4.5-13.8 (156)	24, 15.3, 10.1-22 (156)	58/94 (152)	6 (94)
ANKRD26-RT	48/6	29, 25-30	34, 28-76 (26)	41/1 (42)	27/15 (42)	5/2/27 (34)	4 (42)	3, 7.1, 1.4-19.4 (42)	5, 11.9, 3.9-25.6 (42)	17/23 (40)	0 (23)
bBSS	22/1	32, 28-35	40, 26-65 (15)	16/5 (21)	8/13 (21)	9/4/7 (20)	6 (21)	1, 4.7, 0.1-23.8 (21)	3, 14.2, 3-36.3 (21)	12/3 (15)	0 (3)
mBSS	42/3	29, 25-34	86, 66-105 (33)	37/2 (39)	29/10 (39)	6/4/28 (38)	0 (39)	1, 2.5, 0.1-13.4 (39)	5, 12.8, 4.2-27.4 (39)	19/18 (37)	1(18)
ACTN1-RT	18/1	24, 22-26	72, 55-88 (11)	17/0 (17)	17/0 (17)	0/0/17 (17)	0	0, 0, 0-19.5 (17)	0, 0, 0-19.5 (17)	6/11 (17)	0 (11)
FPD/AML	9/2	27, 21-29	92, 80-105 (4)	7/0 (7)	4/3 (7)	0/1/4 (5)	1 (7)	1, 14.2, 0.3-57.8 (7)	1, 14.2, 0.3-57.8 (7)	3/3 (6)	0(3)
ITGB3-RT	3/0	28, 24-29	82, 58-110 (3)	3/0 (3)	0/3 (3)	1/0/0 (1)	2 (3)	0, 0, 0-70.7 (3)	0, 0, 0-70.7 (3)	1/2 (3)	0 (2)
VWDP	5/0	30, 29-32	110, 58-113 (5)	4/1 (5)	3/2 (5)	2/0/3 (5)	0 (5)	1, 20, 0.5-71.6 (5)	3, 60, 14.6-94.7 (5)	3/0 (3)	0 (0)
GPS	3/1	25, 25-28	47, 40-55 (2)	2/0 (2)	2/0 (2)	2/0/0 (2)	2 (2)	0, 0, 0-84.1 (2)	1, 50, 1.2-98.7 (2)	2/0 (2)	0 (0)
FLNA-RT	1/0	28	82 (1)	1/0 (1)	1/0 (1)	0/0/1 (1)	0 (1)	0, 0, 0-97.5 (1)	0, 0, 0-97.5 (1)	0/1 (1)	0 (1)
TUBB1-RT	1/0	39	48 (1)	0/1 (1)	0/1 (1)	1/0/0 (1)	0 (1)	0, 0, 0-97.5 (1)	0, 0, 0-97.5 (1)	0/0 (0)	0 (0)
VCFS	1/0	33	(0)	1/0 (1)	1/0 (1)	0/1/0 (1)	0 (1)	0, 0, 0-97.5 (1)	0, 0, 0-97.5 (1)	0/1 (1)	0 (1)
CYCS-RT	1/0	28	50 (1)	1/0 (1)	1/0 (1)	0/0/1 (1)	0 (1)	0, 0, 0-97.5 (1)	0, 0, 0-97.5 (1)	1/0 (1)	0 (0)
TOTAL	339/35	28, 25-32	65, 37-85 (188)	272/30 (302)	187/116 (303)	80/46/161 (289)	46 (301)	20, 6.7, 4.1-10.2 (296)	42, 14.1, 10.4-18.6 (296)	122/156 () 278	7 (156)

EBBT: excessive bleeding requiring blood transfusion; AEB: all excessive bleedings; 25th-75th: 25th-75th percentiles; CI: 95% confidence intervals.

reported in 2 infants born by vaginal delivery to 2 *MYH9*-RD mothers with greatly reduced platelet counts (12 and 16 x 10^9/L, respectively). Platelet count was severely reduced in one newborn (7 x 10^9/L) with the same *MYH9* mutation as the mother, while neither testing for *MYH9*-RD nor a platelet count were carried out in the other neonate because he died shortly after birth.

Deliveries

Table 2 describes maternal characteristics at delivery as well as management of childbirth and bleeding events. Platelet count at delivery was available in 188 cases, and comparison with base-line non-pregnant platelet count revealed mild differences (mean platelet count before pregnancy 56 x 10^9/L, at delivery 65 x 10^9/L; P=0.071). Thus, only limited changes in platelet count are expected to occur during pregnancy in patients with ITs.

Prophylactic platelet transfusions were given in preparation for delivery in 46 of 301 evaluable cases, while other prophylactic treatments, consisting of steroids, desmopressin, tranexamic acid or recombinant activated factor VII, were given in 9, 5, 2 and one case, respectively.

Mean platelet count at delivery was lower in women given prophylactic platelet transfusions than in women not receiving this treatment (40 *vs.* 69 x 10^9/L; P<0.001). Similar results were obtained when baseline non-pregnant platelets counts were considered (38 *vs.* 65 x 10^9/L; P<0.001). This indicates that platelet count may have been a parameter used by physicians to determine the need for prophylactic platelet transfusion.

One hundred and sixteen of 303 births were by caesarean section. In the 289 deliveries for which information on pain control was available, general anesthesia was performed in 80 cases (27.7%), and spinal or epidural anesthesia in 46 (15.9%). No bleeding complications related to these procedures were reported.

AEB occurred in 42 cases (14.2% of deliveries, 95%CI: 10.4-18.7) and EBBT in 20 cases (6.8% of deliveries, 95%CI: 4.17-10.2). In case of EBBT, platelet transfusions were given in 6 deliveries, red cell transfusions in 9 and both red blood cell and platelet concentrates in 5. Since the incidence of abnormal bleeding at delivery in the normal population, as evaluated by the amount of blood loss, is 3-7% in high resource countries,[2] the frequency of AEB appears to be higher in ITs than in the general population. Comparison of the need for red blood cell transfusion in our case series is possible with that observed in the general population: fifteen deliveries in women with ITs required erythrocyte transfusions (5.06%, 95%CI: 2.8-8.0), while the need for this treatment ranged from 0.5 to 1.2% in non-thrombocytopenic women.[2,15,16] Altogether, these results indicate that bleeding risk at delivery is increased in ITs.

No women died from complications of childbirth or required hysterectomy to stop bleeding.

Correlations between mothers' features and bleedings at delivery

Some predictors of AEB and EBBT at delivery were identified (Table 3). Considering EBBT at delivery, a trend towards statistically significant association was found with EBBT at previous surgery (OR 4.7, 95%CI: 0.8-26.9), while a significant correlation was found with a history of grade 3 or 4 (OR 5.32, 95%CI: 1.22-23.11) and grade 4 (OR 24.50, 95%CI: 4.75-126.41) of WHO bleeding scale.

EBBT was also significantly associated with a base-line platelet count in the lowest tertile, and a trend towards significance was found between EBBT and platelet count in the lowest tertile at delivery (platelets >49 x 10^9/L). ROC analysis identified platelet counts of 44 and 50 x 10^9/L as the optimal cut offs of platelet counts before pregnancy and at delivery, respectively, for the identification of patients with a higher risk for EBBT. The incidence of EBBT in mothers with platelet counts below these cut-off values before pregnancy and at delivery was 3.92 (95%CI: 1.43-10.70) and 7.61 (95%CI: 1.55-37.60) times higher, respectively, than in patients with higher platelet counts. Both differences were statistically significant.

EBBT was not less frequent in vaginal deliveries than in caesarean sections and was not reduced in women who received prophylactic platelet transfusions prior to delivery. Table 2 shows that the incidence of bleeding requiring blood transfusion was not significantly different in different forms of IT. However, this finding is reliable for *MYH9*-RD, *ANKRD6*-RT, bBSS, mBSS and *ACTN1*-related thrombocytopenia (*ACTN1*-RT) because of the high number of investigated deliveries, while it is not dependable for all other disorders because of the low number of observed childbirths.

A history of surgical bleeding and lower platelet counts also correlated with AEB, though to a lesser extent than with EBBT. As with EBBT, other examined maternal characteristics did not predict AEB at delivery.

Discussion

Inherited thrombocytopenias have long been considered exceedingly rare, but recent advances have facilitated diagnosis and greatly increased the number of reported patients.[17] Although population studies have not yet been performed, it has recently been calculated that the prevalence of ITs in Italy is at least 2.7 in 100,000.[18] The improved knowledge of ITs has also changed our view of their clinical picture. It has been shown that bleeding tendency is mild in the majority of patients and spontaneous life-threatening hemorrhage is uncommon/rare.[11] Nevertheless, hemostatic challenges always need careful attention. Pregnancy and delivery are especially critical because both mothers and affected newborns are at risk of hemorrhage. However, published data are insufficient to provide an evidence-based approach to management during pregnancy and delivery. The present study on 339 pregnancies in 181 women with 13 different ITs provides, for the first time, the opportunity to systematically examine this topic in detail.

Results of our study on the one hand suggest that the course of pregnancy in ITs does not differ from that of healthy women; on the other hand, the risk of bleeding with childbirth appears to be increased in both mothers and neonates.

Neither thrombocytopenia nor bleeding tendency worsened during pregnancy. The incidence of pregnancy loss was superimposable to that observed in healthy women, and the incidence of pre-term birth was not increased in women with ITs. No intrauterine bleeding was reported in the 156 fetuses who inherited IT. However, antepartum gastrointestinal[19] and intracranial bleedings[20] with fatal consequences have been previously described in the fetuses of 2 bBSS mothers. A risk of major bleeding in utero must, therefore, be borne in mind, though such events were not observed in our study cohort. Regarding delivery-related

neonatal bleedings, our data indicate that the risk is low, although fatal hemorrhages may occur. Indeed, only 7 of 156 affected newborns had bleeding. In 5 cases, bleeding consisted of petechiae, but 2 neonates, both born by vaginal delivery to mothers with severe thrombocytopenia due to *MYH9*-RD, died of cerebral hemorrhage. To our knowledge, delivery-related fatal intracranial hemorrhages have not been previously reported in neonates with ITs. The small number of neonates affected by ITs other than *MYH9*-RD does not allow us to exclude a risk of severe neonatal hemorrhage with these conditions, though none were observed in our series. Similarly, we cannot conclude that vaginal delivery is associated with a greater risk of neonatal hemorrhage, because this type of birth was chosen in the vast majority of *MYH9*-RD women, as well as in other forms of ITs. Thus, infants delivered vaginally by severely thrombocytopenic women with *MYH9*-RD must be considered at risk for intracranial bleeding; we cannot exclude the possibility that other forms of IT or caesarean section may expose newborns to similar risk. The incidence of delivery-related maternal bleeding in our case series ranged from 6.8% to 14.2% depending on the criterion used for defining abnormal bleeding. Comparison with healthy women is difficult, because most commonly used definitions of partum-related hemorrhages in the general population rely on the amount of blood loss (>500 mL for vaginal deliveries, and >750-1500 mL for caesarean births),[2] but this information was not available for the majority of our patients. Instead, we adopted two different criteria for increased bleeding: one based on the need to give blood products (EBBT), the other taking into account not only blood transfusions, but also the judgment of the obstetrician that bleeding was excessive (AEB). The former definition may underestimate the occurrence of hemorrhages as defined by the entity of blood loss, because it is conceivable that not all women losing more than 500 mL of blood after vaginal delivery or more than 750 mL after caesarean section received blood transfusions. Also the latter definition risks underestimating the frequency of bleedings because it includes a subjective assessment and it has been shown that

Table 3. Correlations between mother characteristics and bleeding at delivery.

Mothers' characteristics	N. of deliveries	EBBT at delivery				AEB at delivery			
		Events	OR	95% CI	*P*-value	Events	OR	95% CI	*P*-value
EBBT at previous surgery	17	4	4.77	0.85-26.87	0.08	6	1.45	0.36-5.83	0.60
AEB at previous surgery	56	6	2.06	0.69-6.12	0.20	15	2.75	1.15-6.62	0.023
Tertiles of WHO bleeding scale*			0.08		0.31				
1st (0-0)	101	3	1	–	–	11	1	–	–
2nd (1-2)	145	10	2.42	0.65-8.96	0.19	20	1.31	0.53-3.21	0.56
3rd (3-4)	50	7	5.32	1.22-23.11	0.026	11	2.31	0.77-6.97	0.13
WHO bleeding scale*		<0.001		0.06					
0	101	3	1	–	–	11	1	–	–
1	59	2	1.15	0.19-7.06	0.88	6	0.93	0.30-2.83	0.30
2	86	8	3.35	0.87-12.92	0.08	14	1.59	0.60-4.20	0.60
3	36	1	0.93	0.09-9.20	0.95	4	1.02	0.29-3.61	0.97
4	14	6	24.50	4.75-126.41	<0.001	7	8.18	1.80-37.29	0.007
Tertiles of platelet count at delivery				0.09		0.40			
1st (<49 x 10^9/L)	65	7	1	–	–	11	1	–	–
2nd (49-80 x 10^9/L)	66	1	0.12	0.01-1.29	0.080	6	0.13	0.01-1.09	0.06
3rd (> 80 x 10^9/L)	56	2	0.28	0.04-2.00	0.20	8	0.31	0.06-1.54	0.15
Tertiles of platelet count before pregnancy				0.11		0.60			
1st (<39 x 10^9/L)	101	10	1	–	–	17	1	–	–
2nd (39-77 x 10^9/L)	96	8	0.83	0.30-2.27	0.71	14	0.84	0.36-1.96	0.69
3rd (>77 x 10^9/L)	99	2	0.19	0.04-0.90	0.037	11	0.62	0.24-1.59	0.31
Platelet count before pregnancy < 44 x 10^9/L	117	14	3.92	1.43-10.70	0.008	23	2.06	0.99-4.28	0.053
Platelet count at delivery < 50 x 10^9/L	69	8	7.61	1.55-37.60	0.012	14	2.49	1.02-6.02	0.046
Diagnosis of biallelic Bernard-Soulier syndrome	21	1	0.67	0.08-5.58	0.71	3	1.01	0.29-3.47	1.00
Primipara	168	14	1.85	0.71-4.84	0.21	27	1.44	0.79-2.63	0.23
Tertiles of age at pregnancy			0.81		0.31				
1st (15-26)	102	8	1	-	-	18	1	–	–
2nd (27-31)	103	7	0.86	0.33-2.26	0.75	15	0.80	0.35-1.80	0.58
3rd (32-41)	91	5	0.68	0.22-2.15	0.51	9	0.51	0.22-1.21	0.12
Prophylactic platelet transfusion before delivery	44	3	1.01	0.30-3.42	0.99	8	1.47	0.62-3.49	0.38
Vaginal delivery	183	11	0.74	0.31-1.79	0.50	25	0.89	0.44-1.83	0.76

**World Health Organization bleeding scale: grade 0, no bleeding; grade 1, petechiae; grade 2, mild blood loss; grade 3, gross blood loss; grade 4, debilitating blood loss; EBBT: excessive bleeding requiring blood transfusion; AEB: all excessive bleedings; OR: Odds Ratio; CI: confidence intervals.*

visual estimation tends to under-evaluate blood loss at delivery with respect to more accurate measurements.[21] Since the incidence of increased bleeding at delivery in the general population ranges from 3% to 7%,[2] AEB in our case series was higher than normal, while EBBT was at the upper limit of normal range. However, the observation that red blood cell transfusions at delivery were given much more frequently in our patients (5% of deliveries) than in the general population (0.5-1.2%) strongly suggests that bleeding risk is increased in ITs.

Because of this, we searched for mothers' parameters able to predict delivery-related bleedings. EBBT at childbirth was more frequent in women with higher grades of the WHO bleeding scale before pregnancy, and a trend toward statistical significance was found between EBBT at delivery and EBBT at previous surgeries. Also the degree of thrombocytopenia before pregnancy and at delivery was related to EBBT, although with different degrees of statistical significance. Based on this finding, we searched for the cut-off value of platelet count able to predict EBBT by ROC curve analysis, and found that platelet count less than 50 x 10^9/L at delivery and less than 44 x 10^9/L before pregnancy were significantly associated with higher frequency of hemorrhage requiring blood products. Thus, the bleeding tendency before pregnancy and the degree of thrombocytopenia are both important to predict severe bleeding at childbirth. Of note, experts' recommendations for management of pregnancy in patients with immune thrombocytopenia identified platelet count 50 x 10^9/L as the minimum value required for safe delivery.[22,23]

Broadly similar results were obtained in the search for correlations between AEB at delivery in the mothers and their previous bleeding tendency as well as their platelet counts. However, the risk deriving from unfavorable features was lower and had lower statistical significance than for EBBT, probably because the definition of AEB includes a subjective judgment of milder bleeding events.

No other investigated maternal characteristics predicted increased bleeding at delivery. Based on the common notion that severe hemorrhages are frequent on the occasion of hemostatic challenges in patients with bBSS and the previously published data on delivery in these patients,[4] it is surprising that bleeding events at childbirth in our case series were no more frequent in bBSS than in other forms of IT. This unexpected finding could have several explanations. First, the base-line bleeding tendency in our bBSS women was milder than that observed in other series of unselected bBSS patients, as shown by the observation that WHO grade 3 and 4 bleeding were reported only in 3 of our 13 women, while they were described in 7 of 10 patients of a previous case series.[24] It may be that our group of bBSS patients was enriched in forms with mild bleeding tendency because some women with severe bBSS have undergone hysterectomy for heavy menstruation or have been discouraged from having a pregnancy by the fear of bleeding at delivery. Moreover, the frequency of prophylactic platelet transfusions in bBSS women was twice that of women with other ITs, and this may have masked a higher risk of bleeding. The observation that only one AEB (not requiring blood products) was reported in 15 deliveries of bBSS patients not preceded by prophylactic platelet transfusions supports the hypothesis that giving platelets in preparation for delivery may be unnecessary in women with mild forms of bBSS. Finally, the previous systematic review, which was based on case reports and, therefore, was highly susceptible to reporting bias, could have overestimated bleeding risk at delivery.

Another surprising finding was the similar incidence of increased bleeding at delivery in mothers receiving or not receiving prophylactic platelet transfusions, in that this result might suggest that platelet transfusions were ineffective. However, the observation that platelet count was lower in women given transfusions provides a credible alternative explanation and suggests that prophylactic platelet infusions were effective in reducing the incidence of hemorrhage.

Our study has some limitations. First, only a small number of eligible patients with some forms of IT were identified by the participating centers (Table 1), likely reflecting the rarity of these disorders. Creation of larger international registries is required to further improve knowledge of pregnancy outcomes in these rare disorders. Another limitation derives from the failure of automated cell counters to identify very large platelets and the resulting underestimation of platelet count in inherited macrothrombocytopenias, especially bBSS and *MYH9*-RD.[12] It is thus likely that the degree of thrombocytopenia in these conditions was overestimated in our study. Moreover, data were missing in a relevant number of patients enrolled in the study, a limitation inherent to retrospective investigations. Finally, we compared the outcome of pregnancy in women with ITs with that reported in general population. Comparison with non-thrombocytopenic women from these same institutions from the same time periods would be more appropriate, but obtaining the required information from 45 centers in 20 countries seemed to us a hopeless undertaking.

In conclusion, our study showed that delivery-related bleeding risk is higher in ITs than in the general population for both mothers, who may have blood loss requiring blood transfusions, and affected newborns, who may rarely present with fatal intracranial hemorrhage. Nevertheless, delivery occurs without bleeding complications in the vast majority of mothers and neonates. Our study also identified the degree of thrombocytopenia and a history of severe bleeding tendency in the mother as potentially useful parameters to predict the risk of delivery-related bleedings.

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