

# Pregnancy-Associated Thrombocytopenia Revisited: Assessment and Follow-Up of 50 Cases

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Thrombocytopenia detected during pregnancy addresses the issue of its mechanism and of the possible occurrence of neonatal thrombocytopenia. To further investigate these issues, 50 women referred to us because of thrombocytopenia detected during pregnancy (platelet count,  $<150 \times 10^9/L$ ), were extensively studied, as well as their offspring. Among these thrombocytopenic women, we used the threshold of  $70 \times 10^9/L$  to differentiate between mild and severe thrombocytopenia. Whatever the severity of thrombocytopenia, we found biological features of an autoimmune disorder in 48% of the women, and chronic thrombocytopenia in 55%. A familial thrombocytopenia was evidenced in 1 case. These 50 women gave birth to 63 neonates, among whom 24 were thrombocytopenic, either at birth or during the first week of life. Neonatal thrombocytopenia could only be predicted in

multiparous women, on the basis of previous neonatal thrombocytopenia in older siblings, and/or when maternal platelet life span study, performed before pregnancy, had evidenced an autoimmune thrombocytopenia (AITP)-like profile. These results suggest that, in case of pregnancy-associated thrombocytopenia, familial and immunological studies, combined with postdelivery iterative platelet counts, should be performed to properly characterize the thrombocytopenia. Moreover, the platelet count of the neonate should be carefully assessed at birth and during the following days, a platelet life span study should be performed after delivery in the mother, because these two parameters are likely to bring valuable information regarding the forthcoming pregnancies and the risk of neonatal thrombocytopenia.

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**T**HROMBOCYTOPENIA, observed in about 7% of pregnancies, may be related to previously acquired or inherited diseases or to pregnancy-related complications such as pre-eclampsia, sepsis, or obstetrical disseminated intravascular coagulation.<sup>1,2</sup> In 75% of the cases, thrombocytopenia cannot be referred to any of these etiologies. In such cases, pregnancy-associated thrombocytopenia is generally assumed to be secondary to an increased platelet consumption within the placental circulation and/or to hormonal inhibition of megakaryocytopoiesis; it has also been called asymptomatic thrombocytopenia, because it is considered to be devoid of any clinical adverse manifestation in the mother or in the offspring.<sup>3,4</sup> It has recently been defined as a mild thrombocytopenia that resolves spontaneously after delivery and should not be associated with fetal thrombocytopenia.<sup>5</sup> However, several studies have described a fetal and/or neonatal thrombocytopenia occurrence in 4% to 13% of these cases.<sup>6,7</sup> The mechanism of neonatal thrombocytopenia is not elucidated so far and addresses the issue of a possible undetected maternal autoimmunity.<sup>8</sup>

To assess this hypothesis, we performed an extensive study in a selected population of women referred because of thrombocytopenia detected during pregnancy. We found biological features of an autoimmune disorder in 48% of the women of our series; furthermore, thrombocytopenia persisted after pregnancy in 55% of the women.

## PATIENTS

Seventy-five women in whom thrombocytopenia (defined as a platelet count  $<150 \times 10^9/L$ ) had been detected during pregnancy were referred to us by different obstetrical centers. Twenty-five were excluded because information concerning their offspring was lacking or because of loss of follow-up during or after pregnancy. Fifty women who entered the study were investigated either during pregnancy (31 cases) or after delivery (19 cases). At the first visit, they were asked to recall any thrombocytopenic past episode and to bring any platelet count that could have been performed before pregnancy. Women with previous history of autoimmune thrombocytopenia (AITP), systemic lupus erythematosus, or human immunodeficiency virus (HIV) infection were systematically excluded. None exhibited any pregnancy associated complications prone to induce thrombocytopenia, such as sepsis, pre-eclampsia, Hemolysis Elevated Liver Enzymes Low Platelets (HELLP) syndrome, or disseminated intravascular coagulation.<sup>1</sup>

Sixty-four neonates were born to these 50 women; 63 of 64 were evaluated, because 1 who died with a Di George syndrome on day 42 was excluded. Platelet counts were performed either at birth, on umbilical cord or peripheral venous blood (50 cases), or during the first week of life (13 cases), depending on local procedures. When neonatal thrombocytopenia, defined as a platelet count less than  $150 \times 10^9/L$ , had been identified, platelet counts were performed until normalization, whereas clinical and biological studies were performed to further define its mechanism.

## MATERIALS AND METHODS

**Immunological tests.** Assessment of platelet-associated IgG (PAIgG) was performed using isotopic methods.<sup>9</sup> Circulating or associated antiplatelet autoantibodies were identified by immunocapture assays monoclonal antibody-specific immobilization of platelet antigens (MAIPA test)<sup>10</sup> using monoclonal antibodies against platelet glycoproteins (GP) IIb-IIIa, Ib-IX, and Ia-IIa as previously described.<sup>8</sup>

Diagnosis of materno-fetal antiplatelet allo-immunization was assessed by identification of parental platelet antigen incompatibility and screening of maternal serum against both a panel of phenotyped donors' and the father's platelets.

Serum anticardiolipin antibodies were detected using the enzyme-linked immunoassay described by Harris et al.<sup>11</sup> GPL and MPL units were defined as the antibody reactivity of 1  $\mu g/mL$  of purified anticardiolipin IgG or IgM (kindly provided by E.N. Harris, Louisville, KY). Antinuclear antibodies were detected by indirect immunofluorescence on 4- $\mu m$  rat liver sections.<sup>12</sup> Antithyroglobulin antibodies were detected using enzyme-linked immunosorbent assay (ELISA).<sup>13</sup>

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**Isotopic study.** <sup>111</sup>Indium-labeled autologous or heterologous platelets were infused 2 to 16 months after delivery, after verification of adequate contraception and/or of  $\beta$  human chorionic gonadotrophin ( $\beta$ HCG) level less than 5 IU/L.<sup>14</sup> Informed consent was obtained from all patients. Several parameters were studied to define the different patterns of the platelet life span. The mean platelet survival time was calculated using linear and exponential models. Platelet recovery in the circulation was extrapolated from the survival curves to time zero.<sup>15</sup> The respective splenic/precordial and hepatic/precordial activity ratios were calculated on platelet infusion (T0), 30 minutes later (T30), and at maximum (Tmax) and plotted on a graph to show early and late distribution of <sup>111</sup>In-platelets in these organs. A normal platelet life span obtained in 7 healthy volunteers after informed consent had been given was characterized by a mean platelet survival time of 208 hours (range, 192 to 232 hours) and an increment of splenic/precordial sequestration ratio = 1.5 between T30 and Tmax.<sup>8</sup>

A thrombocytolysis evocative of AITP also called an AITP-like profile was defined by a mean platelet survival time of less than 130 hours together with a significant secondary increment of the splenic/precordial

sequestration ratio, with the value at Tmax being more than 1.5-fold the value of the T30 ratio.<sup>16</sup> A profile of hypersplenism was characterized by a mean platelet survival time less than 160 hours, with an immediate increased splenic/precordial sequestration ratio and no further increment after T30.

**Statistical analysis.** Mean and standard deviation (SD) values were calculated for each parameter analyzed.  $\chi^2$ -test was used to compare data between groups.

## RESULTS

**Mothers.** Fifty women who had displayed thrombocytopenia during 63 pregnancies were studied (Tables 1 and 2). The mean nadir of the platelet count during pregnancy was  $69 \times 10^9/L$  (SD,  $29 \times 10^9/L$ ), ranging from  $12$  to  $142 \times 10^9/L$ . In 26 women (32 of 63 pregnancies), the platelet count was less than  $70 \times 10^9/L$ , with a mean nadir of  $46 \times 10^9/L$  (SD,  $14 \times 10^9/L$ ). Systematic inquiries disclosed that thrombocytopenia was already present before pregnancy in 4 women (7 pregnancies) in whom it had been incidentally detected, although not further

**Table 1. Evolution of Biological Parameters Throughout 32 Pregnancies Associated With Severe Thrombocytopenia (Platelet Count  $<70 \times 10^9/L$ )**

Patient No.	Mothers							
	Platelet Nadir $\times 10^9/L$ (during pregnancy)	Platelet Count $\times 10^9/L$ (postdelivery)	Platelet Life Span	PAIgG (+/-)	Antiplatelet Autoantibody (MAIPA test)		Autoimmunity	NNT (+/-)
					Platelet-Associated	Circulating		
3a*	59	100	AITP	+	ND	Neg	Neg	-
3b*	35	ND		-	ND	Neg	Neg	-
6a	30	67	AITP	-	ND	Neg	Neg	+
6b	53	130		-	Neg	Neg	ACA	+
8	60	100	ND	-	ND	Neg	Neg	-
9	35	40	AITP	+	ND	Neg	ACA	-
10	58	201	ND	-	ND	GP Ib-IX	ND	+
12a	42	157	AITP	-	ND	GPIb-IX	Neg	-
12b	65	166		-	ND	GPIb-IX	Neg	-
14	60	135	ND	-	ND	Neg	Neg	-
15	52	248	AITP	-	ND	Neg	ND	+
17	35	167	AITP	-	ND	Neg	Neg	+
22*	64	68	AITP	+	Neg	Neg	Neg	-
23	50	50	N	-	ND	Neg	ND	-
25	35	237	ND	+	Neg	Neg	Neg	-
26	57	190	HS	-	ND	GPIb-IX	Neg	-
28a	69	115	N	ND	ND	ND	ND	-
28b	58	100		-	ND	ND	ND	-
29	40	30	AITP	+	ND	Neg	Neg	+
31a	30	ND	ND	ND	ND	Neg	ND	-
31b	26	95		-	ND	Neg	ACA	-
32	35	ND	ND	+	ND	Neg	Neg	-
37	35	110	AITP	-	Neg	Neg	Neg	+
38	51	174	ND	-	ND	Neg	Neg	-
40	<50	180	HS	-	ND	Neg	Neg	-
41a	30	ND	AITP	+	Neg	Neg	Neg	+
41b	32	103		+	Neg	Neg	Neg	+
42a	50	162	HS	-	ND	Neg	Neg	+
44	60	160	UN	-	Neg	Neg	Neg	-
47	12	35	ND	+	Neg	Neg	Neg	-
48	63	203	HS	-	Neg	Neg	Neg	-
50	50	192	AITP	-	GPIIb-IIIa	Neg	ACA	-

Abbreviations: a, first pregnancy; b, second pregnancy; NNT, neonatal thrombocytopenia; ND, not determined; AITP, AITP-like profile; HS, profile evocative of hypersplenism; N, normal profile; UN, unclassable profile; PAIgG, platelet-associated IgG; GP, glycoprotein; Neg, negative; ACA, anticardiolipin antibody.

\*Previously detected thrombocytopenia.

**Table 2. Evolution of Biological Parameters Throughout 31 Pregnancies With Mild Thrombocytopenia (Platelet Count  $\geq 70 \times 10^9/L$ )**

Patient No.	Mothers							NNT (+/−)
	Platelet Nadir × 10 <sup>9</sup> /L (during pregnancy)	Platelet Count × 10 <sup>9</sup> /L (postdelivery)	Platelet Life Span	PAIgG (+/−)	Antiplatelet Autoantibody (MAIPA test)			
					Platelet-Associated	Circulating	Autoimmunity	
1	90	106	ND	−	ND	GP Ib-IX	ND	+
2a*	90	146	AITP	ND	ND	ND	ND	+
2b*	102	59		ND	ND	ND	ND	+
2c*	71	100		−	ND	Neg	Neg	+
4	88	139	ND	−	ND	Neg	Neg	+
5	71	109	UN	+	ND	Neg	ACA	−
7	70	145	AITP	−	ND	Neg	Neg	−
11	80	167	HS	+	ND	GPIb-IX	ACA	−
13	100	123	ND	−	ND	Neg	ANA	−
16	90	144	AITP	−	ND	GP Ib-IX	Neg	+
18a	105	170	HS	−	Neg	GPIb-IX	Neg	−
18b	110	170		−	Neg	Neg	Neg	−
19a	80	ND	ND	−	ND	Neg	ND	+
19b	70	107		−	ND	Neg	ND	−
20a	112	185	ND	+	ND	GPIb-IX	ANA/anti-SMC	−
20b	124	170		−	ND	Neg		−
21	97	240	N	+	Neg	GPIb-IX	Anti-TG	−
24*	72	111	AITP	−	GPIIb-IIIa	Neg	Neg	+
27	97	180	AITP	+	ND	GPIb-IX	Neg	−
30	89	120	HS	−	ND	Neg	Neg	−
33	103	124	AITP	+	GPIIb-IIIa	Neg	ACA	+
34	70	218	ND	+	ND	ND	Neg	−
35	100	177	ND	+	ND	Neg	Neg	−
36a	96	113	ND	+	Neg	Neg	Anti-TG	+
36b	100	ND		−	Neg	Neg	Anti-TG	+
39	77	ND	ND	−	GPIIb-IIIa	Neg	Neg	+
42b	120	192	HS	−	Neg	Neg	Neg	−
43	142	121	HS	−	ND	GPIb-IX	Neg	−
45	113	160	AITP	−	Neg	Neg	Neg	+
46	80	177	HS	−	ND	Neg	Neg	+
49	116	ND	ND	−	ND	Neg	Neg	−

Abbreviations: a, first pregnancy; b, second pregnancy; c, third pregnancy; ND, not determined; AITP, AITP-like profile; HS, evocative of hypersplenism; N, normal profile; UN, unclassable profile; PAIgG, platelet-associated IgG; GP, glycoprotein; Neg, negative; ACA, anticardiolipin antibody; ANA, antinuclear antibody; Anti-TG, anti-thyroglobulin antibody; anti-SMC, anti-smooth muscle cell autoantibody.

\*Previously detected thrombocytopenia.

investigated, during a preoperative assessment or a long-term follow-up for Hodgkin's disease.

No severe bleeding episode was observed during pregnancy; nevertheless, a specific treatment was administered in 22 cases according to the usual procedures applied in the various centers. This treatment had been initiated early in pregnancy in 4 cases or in the prepartum period in 18 cases. It included either high-dose intravenous IgG (IVIgG; 4 cases), oral steroids (10 cases), or platelet transfusion (1 case). IVIgG had been associated with oral steroids in 3 cases. Furthermore, platelet concentrates had been infused in 4 women after unsuccessful IVIgG and/or oral steroid therapy, due to a severe thrombocytopenia in 1 case, before a cesarean section in 2 cases, and in 1 case of hemorrhagic delivery.

Therapy resulted in a complete correction, as defined by a platelet count greater than  $150 \times 10^9/L$  in 5 cases. There was only a partial response in 13 cases, with a 50% increment of the platelet count in 6 cases or an increment ranging from 20% to 50% in 7 cases. In 4 cases, the treatment failed to increase the platelet count.

A long-term follow-up of the platelet count was performed after delivery in 47 women (55 pregnancies). In 26 women (30 pregnancies) thrombocytopenia was actually chronic, as the platelet count remained less than  $150 \times 10^9/L$  long after delivery (from 2 to 36 months), with a mean nadir of  $101 \times 10^9/L$  (range, 35 to  $146 \times 10^9/L$ ).

Maternal thrombocytopenia recurred or was aggravated during the subsequent pregnancies in all cases, including all 4 multiparous women whose thrombocytopenia had resolved after the first delivery (Tables 1 and 2).

Immunological results are shown in Tables 1 and 2. All of the maternal platelets were sampled for PAIgG (43 during pregnancy). Elevated PAIgG levels ( $>1,000$  IgG/platelet) were observed in 17 cases, 2 of which had received IgG infusion on the days before sampling. It was the only biological abnormality in 7 of 17 cases and was not considered specific. In contrast, a total of 21 women were considered as having biological signs of autoimmunity, because the MAIPA test and/or any other autoantibodies tests resulted positive. Among them, 8 tested iteratively during and after pregnancy were found con-

sistently positive. Six were tested only during pregnancy and 7 after delivery. No difference in frequency of detected abnormalities was observed whatever the period of determination (during and/or after pregnancy). A direct MAIPA test, performed in 17 of 50 cases, evidenced an anti-GPIIb-IIIa autoantibody in 4 women with no antiplatelet antibody detected in the serum. An indirect MAIPA test was performed in the serum of 48 of 50 women sampled during pregnancy in 39 cases. A circulating anti-GPIIb-IX autoantibody was found in 11 cases. An anticardiolipin antibody (IgM >10 U MPL or IgG >15 U GPL) was found in 7 cases and an antinuclear antibody (>1/50) was found in 2 cases. An antithyroglobulin antibody was detected in 2 cases and was related to an autoimmune thyroiditis in 1 of them.

Conversely, 24 women found negative for both the MAIPA test and anticardiolipin or antinuclear antibodies were considered as not having signs of autoimmunity. Five women were considered as not evaluable because only one of these tests was performed and resulted negative.

Platelet life span was studied in 32 of 50 women within 2 to 16 months after delivery (Table 3). Twenty women were

thrombocytopenic at that time, with a platelet count ranging from 11 to  $146 \times 10^9/L$ .

A normal platelet life span was found in only 3 cases. Features of hypersplenism were observed in 9 cases. AITP-like features were found in 18 of 32 cases. Platelet life span features could not be precisely related to any of these patterns in the last 2 cases.

To assess the implications of the severity of thrombocytopenia during pregnancy, two groups of women were constituted according to the platelet count threshold of  $70 \times 10^9/L$  (Table 4): 2 multiparous women had to be excluded because of discordant results in their offspring (see below). Comparing the two groups for maternal and neonatal parameters, there was no difference regarding both the number of mothers diagnosed with chronic thrombocytopenia after pregnancy and the number of thrombocytopenic neonates. Among the 32 evaluated cases, an AITP-like profile was observed in 11 of 17 cases in the group of severe thrombocytopenia as compared with 7 of 14 in the group of mild thrombocytopenia. Surprisingly, biological signs of autoimmunity were found more frequently in the group of

Table 3. Results of Platelet Life Span Performed in 32 Women

Patient No.	Platelet Count ( $\times 10^9/L$ )	Mean Platelet Survival Time (h)	Platelet Turnover ( $\times 10^9/L/d$ )	Splenic/Precordial Sequestration			Profile
				T30	T max	Tmax/T30	
2*	59	17	147	3	17	5.6	AITP
3*	93	107	69	9	16	1.8	AITP
5	102	92	83	7.5	11.5	1.5	UN
6	91	33	74	3.5	14	4	AITP
7	105	49	136	4.5	10.5	2.3	AITP
9	11	4	212	4.5	11	2.4	AITP
11	138	144	83	6.5	8.5	1.3	HS
12	174	102	102	7	11.5	1.6	AITP
15	224	86	141	7	13	1.8	AITP
16	181	55	296	4	7	1.7	AITP
17	230	75	142	4.5	9	2	AITP
18	164	91	122	7	10	1.4	HS
21	223	192	42	4	4	1	N
22*	63	72	52	3.5	7.5	2.1	AITP
23	50	168	20	4	5	1.2	N
24*	111	121	85	5	10	2	AITP
26	112	95	57	4.5	6	1.3	HS
27	173	89	55	5	13	2.6	AITP
28	116	192	24	3	4.5	1.5	N
29	25	32	60	4.5	13	2.9	AITP
30	130	145	39	9.5	9.5	1	HS
33	120	59	142	12	24	2	AITP
37	110	39	277	9.5	26	2.8	AITP
40	146	109	67	6.5	7	1.1	HS
41	102	43	146	7.5	21	2.8	AITP
42	192	124	108	11	11	1	HS
43	121	86	93	4	4.5	1.1	HS
44	150	216	91	10.5	16	1.5	UN
45	160	95	242	6.2	14	2.2	AITP
46	170	144	116	5.5	5.5	1	HS
48	132	84	154	7	10	1.4	HS
50	192	104	133	3.5	7	2	AITP
Control values (n = 7) range	217-356	192-232	36-62	1-4	1-5	1-1.5	

Abbreviations: AITP, evocative profile of autoimmune thrombocytopenia; UN, unclassable profile; HS, evocative profile of hypersplenism; N, normal profile.

\*Previously detected thrombocytopenia.

**Table 4. Comparison of the Data Obtained in the Two Groups of Mothers According to Their Platelet Count (Threshold,  $70 \times 10^9/L$ ) During Pregnancy**

	Platelet Count During Pregnancy	
	$<70 \times 10^9/L$ (n = 25)	$\geq 70 \times 10^9/L$ (n = 23)
Maternal status		
Chronic thrombocytopenia (platelet count $<150 \times 10^9/L$ )	13/24	12/21
AITP-like profile	11/17	7/14
Biological signs of autoimmu- nity	7/22*	14/22
Neonatal thrombocytopenia (platelet count $<150 \times 10^9/L$ )	7/25	10/23

Note that the data are expressed as the number of women but not of pregnancies. The 2 multiparous women whose offspring exhibited discrepant neonatal platelet count have been excluded.

\* $P < .05$ .

mild thrombocytopenia (14 of 22 as compared with 7 of 22;  $P < .05$ ).

**Fetuses and newborns.** Percutaneous umbilical blood sampling was performed in 22 fetuses stemmed from 21 women at gestational ages ranging from 32 to 38 weeks. Whereas no fetal bleeding was observed, fetal bradycardia occurred in 1 case, leading to cesarean section a few hours after sampling. Among the 22 fetuses, 4 disclosed moderate thrombocytopenia, with platelet counts of, respectively, 70, 80, 106, and  $115 \times 10^9/L$

and were delivered without complication, either by cesarean section or by vaginal delivery.

Sixty-three babies were included in the study. Nineteen were born after a cesarean section because of fetal thrombocytopenia, detected by fetal blood sampling in 2 cases, thrombocytopenia observed in the previous siblings in 1 case, maternal thrombocytopenia in 1 case, or an obstetrical reason in 15 cases.

The platelet count was found normal in 39 neonates, which was further confirmed within the first week of life in 25 of them. Thrombocytopenia was found in 24 neonates, either at birth (15 cases) or during the first week of life (9 cases; Table 5). The mean nadir of postnatal platelet count in the 24 thrombocytopenic newborns was  $52 \times 10^9/L$  (range, 13 to  $140 \times 10^9/L$ ) and was reached on day 4 (range, 0 to 15 days). Only 1 of the 24 thrombocytopenic newborns displayed hemorrhagic symptoms (petechiae and a scalp hematoma) after a vaginal delivery and was treated by oral steroids (1 mg/kg/d and tapered) until day 69, when the platelet count increased to  $80 \times 10^9/L$ . The platelet count at birth was  $75 \times 10^9/L$  and reached a nadir of  $13 \times 10^9/L$  on day 15.

Treatment with IVIgG (1 g/kg/d  $\times 1$  or 0.4 g/kg/d  $\times 5$ ) was performed in 10 cases and resulted in a complete correction in 4 cases or in a transient efficacy in 2 cases. In the 4 remaining cases, data were not available. Thrombocytopenia resolved spontaneously in 2 cases. Evolution was favorable in all cases, with a normalization of platelet count within 11 days (range, 8 to 25 days) in the 8 cases in which it could be assessed.

A nonimmune neonatal pathology that could account for

**Table 5. Neonatal Parameters in the 24 Thrombocytopenic Neonates**

Patient No.	Platelet Count $\times 10^9/L$		Nadir (day)	Normalization of Platelet Count (day)	Treatment	Associated Pathology
	At Birth	At Nadir				
1	62	40	(10)	ND	ND	None
2a	59	15	(14)	ND	ND	None
2b	ND	16	(3)	ND	ND	None
2c	112	43	(4)	ND	IVIgG	None
4	193	80	(5)	(8)	IVIgG	Materno-foetal infection
6a	160	16	(4)	ND	IVIgG	None
6b	25	25	(0)	(16)	IVIgG	None
10	49	49	(0)	(9)	IVIgG	None
15	123	90	(4)	(12)	ND	None
16	17	14	(5)	(24)	IVIgG	None
17	219	105	(5)	(8)	ND	None
19a	360	100	(1)	ND	None	IUGR
24	140	ND	ND	ND	None	Viral infection
29*	75	13	(15)	(>68)	OS	None
33	>150	20	(7)	(10)	IVIgG	None
36a	70	20	(1)	ND	IVIgG	None
36b	24	24	(0)	ND	IVIgG	None
37	ND	37	(3)	ND	None	None
39	ND	45	(5)	ND	ND	None
41a	128	46	(3)	ND	IVIgG	None
41b	105	45	(2)	ND	None	None
42a	250	93	(5)	ND	ND	None
45	103	103	(0)	ND	None	None
46	90	90	(0)	ND	None	None

Abbreviations: a, first neonate; b, second neonate; c, third neonate; ND, not determined; IVIgG, intravenous IgG; OS, oral steroids; IUGR, intrauterine growth retardation.

\*Bleeding symptoms (petechiae and scalp hematoma).

neonatal thrombocytopenia was found in 3 cases: 1 case of neonatal staphylococcus infection, 1 neonatal Rotavirus infection, and 1 intrauterine growth retardation.<sup>17</sup>

A parental human platelet antigen incompatibility was found in 5 of the 11 cases in which it was assessed. However, despite the presence of thrombocytopenia in 3 newborns, the diagnosis of maternofetal alloimmunization could not be ascertained, due to the absence of detectable alloantibody in the mother's serum.

To find out predictors of neonatal thrombocytopenia, two groups of neonates were constituted according to their platelet count and compared regarding siblings' platelet counts and maternal parameters (Table 6). The offspring of multiparous women were consistently either thrombocytopenic or not thrombocytopenic in 10 of 12 cases. In these 10 cases, we found the platelet count to be normal or decreased in the same proportion in all siblings. This finding supports the hypothesis of the predictive value of this parameter ( $P < .05$ ), although in a small subset of cases.

Discrepancy in the 2 remaining cases was as follows. In 1 case, neonatal thrombocytopenia in the first-born was most probably related to intrauterine growth retardation (birth weight, 1,980 g in a full-term newborn), whereas the sibling had a normal platelet count both on percutaneous umbilical blood sampling and at birth. In the last case, antenatal platelet count was found within the normal range in each of the 2 successive siblings. However at birth, the firstborn had exhibited a moderate thrombocytopenia with a platelet nadir on day 5, whereas the second one had a persistent normal platelet count up to day 3.

When excluding the 2 cases discussed above, maternal chronic thrombocytopenia was associated with neonatal thrombocytopenia in 11 of 16 women who delivered thrombocytopenic neonates as compared with 14 of 29 who did not (Table 6). An AITP-like profile and neonatal thrombocytopenia in the previous siblings were significantly more frequently associated with the occurrence of neonatal thrombocytopenia (11 of 12 compared with 7 of 19 and 4 of 4 compared with 0 of 6, respectively). Conversely, the occurrence of neonatal thrombocytopenia did not correlate with the severity of the maternal gestational thrombocytopenia.

**Table 6. Data Considered as Possibly Predictive of Neonatal Thrombocytopenia**

	No. of Mothers Who Delivered Neonates With Platelet Count	
	<150 × 10 <sup>9</sup> /L (n = 17)	≥150 × 10 <sup>9</sup> /L (n = 31)
Maternal status		
Platelet count <70 × 10 <sup>9</sup> /L	7/17	16/31
Chronic thrombocytopenia (platelet count <150 × 10 <sup>9</sup> /L)	11/16	14/29
AITP-like profile	11/12*	7/19
Biological signs of autoimmu- nity	8/16	13/28
Previous newborns (platelet count <150 × 10 <sup>9</sup> /L)	4/4*	0/6

The 2 multiparous women whose offspring exhibited discrepant neonatal platelet count have been excluded.

\* $P < .05$ .

DISCUSSION

Thrombocytopenia, when detected during pregnancy, addresses the issue of a possible related autoimmunity. Most of the studies performed hitherto aimed at identifying, among maternal thrombocytopenias, those of immune origin and at defining criteria predictive of severe fetal thrombocytopenia.<sup>7,18</sup> However, both specific diagnostic tools of an immune origin of thrombocytopenia in the mother and predictive maternal markers of fetal thrombocytopenia during pregnancy are still missing.

The present work was designed to better understand the mechanisms of maternal thrombocytopenia during pregnancy and its consequences in the offspring in a small subset of thoroughly investigated women. This group of patients referred to a highly specialized center does not reflect the overall population of thrombocytopenic pregnant women. However, the following conclusions can be reached.

(1) Maternal studies when performed in this group of thrombocytopenic women showed asymptomatic autoimmunity in 21 of 44 cases. Whether it can evolve towards a symptomatic autoimmune disorder is yet unknown. The follow-up is less than 5 years in our study, which does not allow any definite conclusion regarding this issue.

However, these results confirm that some pregnancy-associated thrombocytopenia may be of immune origin,<sup>3</sup> with a risk of neonatal thrombocytopenia.

(2) The diagnosis of familial thrombocytopenia, easy to achieve, was established in 1 of our 50 cases. It should be systematically searched for before proposing costly and invasive investigations in a pregnant woman with thrombocytopenia, because no maternal or neonatal bleeding complications have ever been reported in most of familial thrombocytopenias (such as May-Hegglin syndrome or Mediterranean thrombocytopenia).<sup>19</sup>

(3) Thrombocytopenia detected during pregnancy did not resolve after delivery in 26 of 47 cases, indicating that 55% of them were actually chronic thrombocytopenia incidentally detected during pregnancy rather than pregnancy-associated thrombocytopenia. Moreover, in our hands, the platelet count during pregnancy was not a reliable predictive marker of the evolution of the maternal disease or of the occurrence of neonatal thrombocytopenia: among women with mild thrombocytopenia (platelet count within 70 to 150 × 10<sup>9</sup>/L), 43% delivered thrombocytopenic neonates and 57% had chronic thrombocytopenia. Furthermore, 64% displayed biological signs of autoimmunity and 50% had an AITP-like profile. It should be noted that all 4 women whose thrombocytopenia had been detected before pregnancy displayed an AITP-like profile. The diagnosis of gestational thrombocytopenia, according to the guidelines of George et al,<sup>5</sup> could be ascertained after delivery in only 8 of 50 cases. However, among these 8 women, 5 displayed biological signs of autoimmunity, associated in 1 case with an AITP-like profile. Pregnancy-associated thrombocytopenia can therefore be a misleading terminology that should not be used unless platelet count is found to be normal in the months after delivery. The diagnosis of pregnancy-associated thrombocytopenia is impossible to ascertain in primiparous women in the absence of previous platelet count determination. Further-

more, immunological studies should be performed to detect hidden autoimmunity.<sup>8</sup>

(4) As previously shown,<sup>7,20</sup> we did not find any statistical correlation between the occurrence of neonatal thrombocytopenia and any of the following maternal parameters: platelet count during pregnancy, evaluation of PAIgG, and characterization of circulating and platelet-associated autoantibodies. Furthermore, no difference was observed in the neonates whether or not mothers had received a specific treatment aimed at increasing the platelet count during pregnancy. However, among the 4 women who displayed platelet-associated anti-GPIIb-IIIa autoantibodies, 3 delivered thrombocytopenic newborns. A recent study suggested that circulating anti-GPIIb-IIIa autoantibodies were likely to be more frequently associated with AITP than with gestational thrombocytopenia but could not be conclusive due to the small number of patients.<sup>21</sup> Likewise, in our study, the question of whether platelet-associated anti-GPIIb-IIIa autoantibody could be associated with hidden autoimmunity remains speculative.

In women found to be thrombocytopenic during pregnancy, we think that a follow-up of platelet count after pregnancy, which has never been extensively achieved,<sup>22</sup> would most probably provide some help in evaluating the risk of neonatal thrombocytopenia in subsequent pregnancies. Indeed, the women of our series displaying chronic thrombocytopenia after pregnancy had, to some extent, delivered more frequently thrombocytopenic newborns (11 of 16 v 14 of 29). This might be of interest when the previous siblings' platelet count is not available.

(5) In contrast, two parameters in multiparous women significantly correlated with the occurrence of neonatal thrombocytopenia. First, the maternal platelet life span, as an AITP-like profile is significantly more often found in the group of women who delivered thrombocytopenic neonates. Unfortunately, it cannot be performed during pregnancy and the results can only be used for subsequent pregnancies. Second is the notion of neonatal thrombocytopenia in a previous sibling. It confirms previous studies showing that, when neonatal thrombocytopenia cannot be ascribed to any recognized cause, its recurrence is likely in the forthcoming siblings.<sup>23</sup>

(6) Because of the postnatal decrease of platelet count observed in most cases, severe neonatal thrombocytopenia may be delayed, occurring a few days after birth. This could account for the low incidence of neonatal thrombocytopenia reported in the offspring of thrombocytopenic women when the platelet count is only performed at birth.<sup>3,4,18</sup> Moreover, 9 of the 24 thrombocytopenic neonates of our series had a normal platelet count at birth, which suggests that, in the offspring of thrombocytopenic women, the platelet count should be checked not only at birth, but also within days 3 to 5. We found that the nadir of thrombocytopenia was reached later than previously reported.<sup>18</sup> This may be due to the cases in which sequential platelet counts were performed only once a week and emphasizes the need of platelet count assessment several times a week in thrombocytopenic neonates until recovery.

Finally, when thrombocytopenia has been detected during pregnancy, whatever the maternal platelet count, and awaiting larger prospective studies based on the overall population of pregnant women to confirm our results, we suggest the following: (1) a familial study should be undertaken, to rule out a

familial thrombocytopenia; (2) an immunological study should be performed to detect an asymptomatic maternal autoimmune disorder; (3) the platelet count of the newborn should be performed at birth and repeated twice during the first week of life; (4) iterative maternal platelet counts should be achieved within the 6 months after delivery to detect chronic thrombocytopenia; (5) in our experience, platelet life span study resulted to be of great interest even when platelet count had returned to a normal level, because it led us to detect a compensated thrombocytolysis in a noticeable number of patients; and (6) neonatal thrombocytopenia is most likely to recur in the offspring of a woman who gave birth to a first thrombocytopenic newborn and/or when the maternal life span study is in favor of an AITP-like profile.

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