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THROMBOCYTOPENIA AND PREGNANCY

TROMBOCITOPENIA E GRAVIDANZA

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Abstract

Gestational thrombocytopenia (GT) is commonly observed in pregnancies with otherwise limited obstetric and hematologic complications.

However, few data are available on the natural history of the disease and on the recurrence of thrombocytopenia in subsequent pregnancies.

37 consecutive patients with GT were enrolled in a prospective study, with a total of 36 pregnancies observed. Vaginal delivery was carried out in 33/41 (80%); two patients were transfused with packed red cells for obstetric hemorrhage (post-partum uterine atony).

Mothers and their related foetuses- newborns were evaluated retrospectively for symptoms and/or signs of external and internal haemorrhage throughout pregnancy and early puerperium, even in relationship with mode of delivery (caesarean section versus spontaneous vaginal delivery). This study confirms, in accordance to literature, that all observed cases of GT have an uncomplicated course with no related perinatal and maternal morbidity even in patients with initial platelet count < 75.000/ml regardless of the route of delivery.

The Authors conducted a retrospective study concerning maternal platelet count fluctuation during pregnancy and puerperium and its correlation with the newborn's platelet level in a group of 36 patients treated at the haematology-clinic of the Santo Bambino Hospital, c/o Azienda Ospedaliero-Universitaria Policlinico-Vittorio Emanuele, Catania.
These patients, with gestational thrombocytopenia (GT), were rolled over a 4-year period, from January 2006 to December 2009.

Abstract

La Trombocitopenia gestazionale (GT) è comunemente osservata nelle gravidanze con complicanze ematologiche.
Tuttavia, sono disponibili pochi dati sulla storia naturale della malattia, e sulla ricorrenza di trombocitopenia in gravidanza.
37 pazienti con GT sono stati arruolate in uno studio retroprospettivo, con un totale di 36 gravidanze osservate. Il parto vaginale è stata effettuato in 33/41 (80%), a due pazienti sono stati trasfusi globuli rossi per emorragia (post-partum atonia uterina) (13).
Le madri e i loro feti-neonati sono stati valutati retrospettivamente per i sintomi e/o segni di emorragia esterna ed interna per tutta la gravidanza e puerperio, anche in rapporto con la modalità del parto (cesareo vs parto vaginale).
Questo studio conferma secondo i dati della letteratura che tutti i casi osservati di GT hanno un decorso senza complicazioni, senza morbilità perinatale e materna correlata, anche in pazienti con iniziale conta piastrinica <75.000/ml.
Lo studio retrospettivo ha registrato la fluttuazione della piastrinemia durante la gravidanza e il puerperio e la sua correlazione con il neonato in un gruppo di 36 pazienti seguite dal centro di ematologia-clinica dell'Ospedale Santo Bambino, c/o Azienda Ospedaliero-Universitaria Policlinico-Vittorio Emanuele, Catania.
Tali pazienti, affette da piastrinopenia gestazionale (GT), sono state arruolate in un periodo di 4 anni, dal gennaio 2006 al dicembre 2009.

Background

Gestational thrombocytopenia (GT) is commonly observed in pregnancies with otherwise limited obstetric and hematologic complications.
Thrombocytopenia is defined as a platelet count below 150 x 10^9/l, caused by accelerated platelet destruction or decreased production. It is classified as mild with a platelet count of 100–150 x 10^9/l, moderate at 50–100x10^9/l and severe with less than 50x10^9/l (1).
Thrombocytopenia is second only to anaemia as the most common hematologic abnormality during pregnancy (2).
Indeed, a platelet count <150x10^9/l can be observed in 6 to 15% of pregnant women at the end of pregnancy. Thrombocytopenia is usually moderate (<100 x10^9/l in only 1% of women) and often incidentally detected on routine blood count (3).
Gestational thrombocytopenia (GT) is considered the most prevalent cause of thrombocytopenia during pregnancy accounting for about 75% of cases (1).
The etiology is unknown, but it is considered to be due to the relative hemodilution of pregnancy, amplified by the capture or destruction of platelets in the placenta (4, 5, 6).
GT is considered a minor form of thrombocytopenia, with no substantial risk of hemorrhage for both the mother and the infant.
Gestational thrombocytopenia is characterized by:

- asymptomatic, mild thrombocytopenia (platelet count >70x10^9/l);
- no past history of thrombocytopenia (except during a previous pregnancy);
- occurrence during the 3rd trimester;
- no fetal / neonatal thrombocytopenia;

- spontaneous postpartum resolution.

Thrombocytopenia can also be associated with several diseases, either pregnancy-related or not, such as preeclampsia and HELLP syndrome (haemolysis, elevated liver enzymes, low platelet count), which represents about 18% of cases, and idiopathic thrombocytopenic purpura (ITP), which is found in about 5% of cases (7). Some rare conditions, such as thrombotic thrombocytopenic purpura, haemolytic uremic syndrome, disseminated intravascular coagulation and others account for about 2% of the total (8, 9) (table 1).

Table 1 - *Causes of thrombocytopenia in decreasing order of frequency during pregnancy*

– Incidental or gestational thrombocytopenia
– Pseudothrombocytopenia (laboratory artifact with EDTA anticoagulant)
– Disorders with increased platelet consumption
– Immune thrombocytopenic purpura
– Pregnancy induced hypertension / HELLP syndrome
– Thrombotic thrombocytopenic purpura
– Hemolytic uremic syndrome
– Infection-associated (HIV, malaria)
– Drug-induced (heparin, sulphonamides, penicillin, rifampicin, quinine)
– Systemic lupus erythematosus
– Antiphospholipid syndrome
– Disseminated intravascular coagulation
– Amniotic embolism
– Disorders with reduced platelet production
– Congenital trombocitopenia
– Aplastic anemia
– Leukaemia
– Drug-induced
– Myelodysplasia

The Authors present here the results of a retrospective study concerning maternal platelet count fluctuation during pregnancy and puerperium and its correlation with the newborn's platelet levels in a group of 36 patients referred to the haematology-clinic for gestational thrombocytopenia and who delivered in the same Hospital during a period of four years.

Methods

Between January 2006 and December 2009, 36 patients with GT (mean gestational age at diagnosis 5 months ± 3 months), who delivered at the Santo Bambino Hospital - c/o Azienda Ospedaliero-Universitaria Policlinico-Vittorio Emanuele, Catania, Italy - , were enrolled in this study, after carefully excluding other possible causes of this condition, and evaluated retrospectively. GT was defined as an asymptomatic thrombocytopenia occurring during gestation, in patients with a normal platelet count at the beginning and or immediately before pregnancy and without antiplatelet-antibodies. The presence of EDTA-dependent pseudothrombocytopenia was ruled out by performing platelet count also in samples anticoagulated with sodium heparin and trisodium citrate and by examination of a May-Grunwald stained peripheral smear.

A maternal platelet count was determined at least three times during pregnancy and once after delivery in each enrolled patient and at least once in every relative newborn at birth (first time on cord blood). All patients underwent specific tests for the presence of antiplatelet- autoantibodies.

Maternal thrombocytopenia was pharmacologically treated only for platelet count ≤ 90.000/ml with the following drugs: vitamin C (1-2,5 g/die) and tranexanic acid (*tranex*) 2-2.5 g/die, until 3-4 hours before delivery and for two days after birth.

When maternal platelet count was between 50.000 and 60.000/ml, prednisone (*deltacortene*) 0,5-1 mg/kg/ die was administered antenatally for about 30 days.

Mothers and their related foetuses-newborns were evaluated retrospectively for symptoms and/or signs of external and internal haemorrhage throughout pregnancy and early puerperium, even in relationship with mode of delivery (caesarean section versus spontaneous vaginal delivery).

Results

A total of 36 patients were retrospectively followed, (22 primigravida).

The mean age was 30 ± 2 years.

Only 6 women had developed thrombocytopenia in a previous pregnancy (table 2).

Table 2

Characteristics of patients	n	%
Primigravide	22	7.92
Multiparous	14	5.04
Previous gestational thrombocytopenia	6	2.16
Spontaneous delivery	21	7.56
Caesarean section	15	5.4

About 45% of the enrolled patients had a caesarean delivery (however only in 1 case, patient 14, table 4, the clinical indication was merely the significant maternal thrombocytopenia and the suspect of a concomitant severe fetal thrombocytopenia by the attending obstetrician, although no maternal antiplatelet-autoantibodies had been identified in this case).

The mean gestational age at the time of diagnosis was 12 ±3 weeks for the 6 women with a previous history of gestational thrombocytopenia and 28±3 weeks in all the other patients (table 3).

Table 3 *- Gestational age at diagnosis*

First onset GT	History of previous GT
28 ±3 weeks	12±3 weeks

Initially, when GT was diagnosed in the 36 studied patients, the average platelet count was at the lowest level, 101(± 26.3) x109/l, it increased to 108 (±18.8) x109/l subsequently during pregnancy and it went further up, 129 (± 27.3.) x109/l, at the time of delivery, reaching the highest level in puerperium: 154 (± 27.9) x 109/l (figure 1 and table 4).

Figure 1 - *Average maternal platelet count fluctuation*

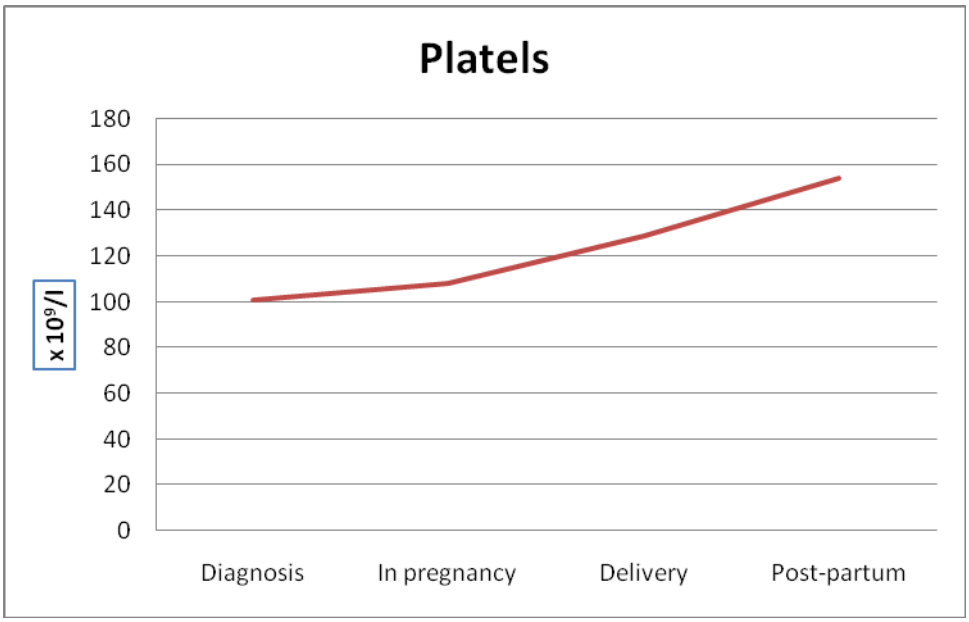

Table 4 - *Maternal and neonatal platelet count: absolute values*

CASE	PLATELED COUNT AT TIME OF DIAGNOSIS	PLATELED COUNT DURING PREGNANCY	PLATELED COUNT AT TERM	PLATELED COUNT PUERPERAL	PLATELED COUNT NEWBORN
1	91	85	90	143	150
2	100	130	150	165	165
3	90	80	90	90	140
4	147	100	103	138	135
***5**	72	100	90	85	150
6	129	100	121	128	165
7	81	87	93	139	150
8	140	113	145	160	180
9	103	115	137	146	150
10	100	110	103	120	110
11	106	100	95	130	142
12	95	98	100	100	130
13	110	100	98	145	154
***14**	41	33	70	90	**72**
15	104	96	90	110	176
16	140	147	135	167	170
17	91	90	103	90	158
18	128	130	107	159	191
***19**	70	90	92	110	154

20	148	90	107	178	143
21	110	89	93	123	178
22	100	116	92	125	123
***23**	92	75	110	112	154
***24**	81	54	108	125	193
25	95	91	114	110	149
26	80	110	100	98	198
27	83	86	108	110	174
28	76	90	100	125	157
***29**	70	85	95	100	187
30	115	110	130	135	145
31	140	147	144	156	164
32	130	160	120	188	149
33	100	108	110	138	152
34	140	144	130	182	190
35	101	120	133	132	178
***36**	53	54	97	126	**80**

* pt with at least one platelet count ≤75 x109/l

The search for antiplatelet antibodies was negative in all women.

Table 5 - *Treatment of thrombocytopenia and type of delivery*

CASE	TROMBOCITOPENIA PRIOR TO PREGNANCY	TREATMENT DURING PREGNANCY	DELIVERY TYPE	AUTOANTIBODY
1	N	N	SVD	N
2	N	N	SVD	N
3	N	Y	CS	N
4	N	N	SVD	N
***5**	N	Y	SVD	N
6	Y	N	SVD	N
7	N	Y	SVD	N
8	N	N	CS	N
9	N	N	CS	N
10	Y	N	SVD	N
11	N	N	CS	N
12	N	N	SVD	N
13	N	N	CS	N
***14**	N	Y	CS	N
15	Y	N	SVD	N
16	N	N	SVD	N
17	N	Y	CS	N
18	N	N	SVD	N
***19**	N	Y	SVD	N
20	N	N	SVD	N
21	N	Y	CS	N
22	N	N	SVD	N
***23**	Y	Y	CS	N
***24**	Y	Y	SVD	N
25	N	N	SVD	N
26	N	N	SVD	N
27	N	Y	CS	N

28	Y	Y	SVD	N
***29**	N	Y	CS	N
30	N	N	CS	N
31	N	N	SVD	N
32	N	N	CS	N
33	N	N	SVD	N
34	N	N	CS	N
35	N	N	CS	N
***36**	N	Y	SVD	N

Y: yes; N: no; CS: cesarean section; SVD: spontaneous vaginal delivery. ;
*: pt with at least one platelet count ≤ 75 x10^9/l

Women during pregnancy didn't show any sign of hemorrhage and were given a vitamin supplementation (vitamin C), and tranexanic acid only in the presence of platelet count ≤90 x109/l, and deltacortene (0.5-1 mg/kg/ die) for platelet count between 50.000 and 60.000/ml.

Fetal-neonatal bleeding symptoms were not observed, and only two cases of mild transitory thrombocytopenia were recorded, as reported in table 6.

Table 6 - *Maternal thrombocytopenia and neonatal complications*

CASE	NEONATAL COMPLICATIONS
1	N
2	N
3	N
4	N
o ***5**	N
6	N
o **7**	N
8	N
9	N
10	N
11	N
12	N
13	N
o ***14**	MILD ASYMPTOMATIC TROMBOCITOPENIA
15	N
16	N
o **17**	N
18	N
o ***19**	N
20	N
21	N
22	N
o ***23**	N
o ***24**	N
25	N
26	N
o **27**	N
o **28**	N
o ***29**	N
30	N
31	N

32	N
33	N
34	N
35	N
o ***36**	MILD ASYMPTOMATIC TROMBOCITOPENIA

*: pt with at least one platelet count ≤ 75 x10^9/l ; o: therapy during pregnancy; N: no complications

Discussion

Thrombocytopenia has been more commonly diagnosed in pregnant women in the last 20 years. It may result in bleeding into mucous membranes presenting as petechiae, ecchymosed, epistaxis, gingival bleeding etc. Moreover, bruising, hematuria, gastrointestinal bleeding and rarely intracranial hemorrhage can occur (10).

The diagnosis of ITP is very difficult during pregnancy because its presentation may closely resemble gestational thrombocytopenia (11, 12).

The diagnosis of ITP should be suspected in case of:

- thrombocytopenia discovered before the 3rd trimester or present before pregnancy;
- platelet count <75 x10^9/l during pregnancy (in our series 7 cases);
- presence of autoantibodies (no cases reported in our series);
- persistence of thrombocytopenia postpartum (sometimes even thrombocytopenia due to ITP may promptly normalize after delivery).

The Authors found that, despite the defining criteria, GT may include cases with moderate (n=6) and severe (n=1) maternal thrombocytopenia and, despite the absence of antiplatelet-autoantibodies, it may be incidentally associated with mild neonatal thrombocytopenia: 2 cases in this series.

The present study confirms that all observed cases of GT have an uncomplicated course with no related perinatal and maternal morbidity even in patient with initial platelet count < 75.000/ml, independently from the mode of delivery.

Conclusion

In case of gestational thrombocytopenia, a complete normalization of maternal platelet count should be expected during the postpartum period, even if a diagnosis of a concomitant incidental neonatal thrombocytopenia cannot be excluded.

No intervention, such as a foetal platelet count or caesarean section, is necessary. Periodic platelet counts, either once a trimester or every month, are recommended depending on the level of thrombocytopenia.

In cases of thrombocytopenia ≤ 90.000/ml patients should be given drugs such as: vitamin C (1-1.5 g/die) and tranexanic acid (*tranex*) 2-2.5g/die to improve platelet count.

In the past, it was common practice to perform caesarean section on mothers with severe thrombocytopenia and presence of circulating antiplatelet autoantibodies to lessen the risk of neonatal intracranial haemorrhage due to the trauma of vaginal delivery, especially with foetal platelet counts < 50 x10^9/l.

In the above clinical scenario , however, caesarean delivery has not been proved to decrease the incidence of either maternal and or neonatal haemorrhage and of course this is particularly true in case of GT as the present study demonstrates.

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