Pit Falls in the Management of Neonatal Thrombocytopenia "Clinical audition"

Ahmed Elgadra,* Huda Elnaji,*

Can a thrombocytopenic (TP) mother damage the brain of her baby?

Sure she can !!

Neonatal Thrombocytopenia TP is a common clinical problem and can cause a lot of neurological damage to the newborn babies.
The normal platelet count of all healthy newborn babies, regardless of gestational age, should be 150.000/ul and above,[1-4] and less than this represent thrombocytopenia, just as in older children and adults.

At birth, TP is present in 1-5% of newborns, "5-7" and severe TP (plat count < 50,000/ul occurs in 0.1- 0.5%.[7-11]

About 8% of preterm and 6% of all neonates admitted to SCBU had severe TP[15] and are at high risk of hemorrhage.

Recently, a five-day-old baby was admitted to SCBU with jaundice, but the investigation revealed very low plat count 22,000/ul. Apart from jaundice, the baby was well and no sign of bleeding disorder was present.

Going back to his birth history and his mother past medical history, we found out that the mother was admitted to the medical ward when she was pregnant in the 6th month because of TP, Her plat count was 60,000/ul, and she was kept in hospital for one month. No treatment was given, such as steroid, IV immunoglobulin; only before discharge she was given plat transfusion.

No previous history of idiopathic thrombocytopenia, SLE, drugs or splenectomy was noticed.

Her first pregnancy went well without any problems and she delivered a healthy full term baby girl, who is now three and a half years of age.

Her second pregnancy went well, too and she went to work at term. She delivered a full term baby boy vaginally with vertex presentation. No resuscitation was required at birth. The weight at birth was 3.9 kg and head circumference was 36cm.

The baby was admitted to SCBU at Jamahiriya Hospital for one day. His plat count was 116,000/ul, so he was discharged the next day.

Checked again at day 3, mild jaundice was noticed but no petechial rash or bruises were seen, so plat count was not checked. Again the baby was sent home with no follow up arrangements.

The baby was presented at day 5 to Children Hospital because of deep jaundice, so he was admitted to SCBU. On examination, he has had deep jaundice but no signs of bleeding problems. The plat count was checked and was 22,000/ul. USS of the brain did not show any signs of 1C bleeding and his HC was 36cm, abdominal USS → normal.

The baby was kept in hospital for one week and was treated with phototherapy. He was discharged home in good condition with a follow up appointment after 3 days.

At day 16 of age, the mother brought the baby to the neonatal outpatient department because of fever and irritability.

The baby was admitted again to SCBU. He was unwell and looked sick. His body temperature was 39, and his skin showed few petechial rash over his limbs and trunk but no bruises were seen.

Head examination revealed a boggy soft swelling over the occipet and HC has increased to 39cm (Fig.1).

Full septic screen was done and IV antibiotics courses were started. Blood and plat transfusion were given and Methylpredenisolone was started the next day.

Unfortunately, Sandoglobulin was not available at the time of admission. Plat count started to rise gradually and reached 88,000/ul with plat transfusion and Methylprednisolone,

*) Neonatal department Al-Fateh Children Hospital, Benghazi, Libya.

but jumped to 209,000/ul two days after Sandoglobulin course was started and continued for 5 days. The plat count rose to 588,000/ul at the end of Sandoglobulin course.

At day 21 of age "before Sandoglobulin course", the baby developed a generalized fit which lasted for few minutes and was terminated by IV Phenytoin and Phenobarbitone.
CT of the brain showed marked dilatation of lateral ventricles with evidence of bleeding.
The baby condition deteriorated and started to show neurodevelopmental sequale.
The head continued to increase in size which eventually required a shunt. The baby clotting screen was normal all the times.

Discussion:
The main fetal risk of maternal TP is intracranial haemorrhage, but there is no consensus about how to safely minimize or avoid this risk.[17-18]

The plat count in affected babies usually falls in the first few days of life and the maximum risk period is 2-3 day after delivery.

Some of the pit falls we made during the management of this baby were:
- √ Monitoring the baby closely with a daily check of plat count for one week until the plat count returns to normal was not carried out.
- √ **A**lso, we did not realize that plat count of 116,000/ul at birth was abnormal and represented thrombocytopenia.[1-4]

As most babies found to have an ICH, which can occur prior to birth in about 10-15% secondary to maternal autoimmune disorder, have had plat count of < 30,000/ul.
We did not initiate treatment, but took the decision of 'wait & see' as long as the thrombocytopenic baby has no signs of bleeding.

It is a common practice to treat any neonate with severe TP "plat count <30,000/ul" with immunoglobulin regardless of whether or not there is evidence of bleeding.[16]

There is no clear evidence that this approach is of benefit, or that the threshold level of 30,000/ul is appropriate.

There is much controversial concerning treatment of babies with low plat count.

Our baby-sample has had low plat count 22,000/ul, which was accidentally discovered during the investigation of hyperbilirubinemia at day 5. We had waited until the baby was 16 days of age and had ICH, before we started treatment, which unfortunately was not available at the time of admission.

So what was the cause of maternal thrombocytopenia??
This question should be answered by a physician and obstetrician.
Was it gestational TP??
- ■ Gestational TP occurs in 4-6% of pregnant women.

According to the American college of obstetricians and gynecologist "1999", there are several characteristics of gestational TP such as:
- Plat count is usually >70,000/ul.
- Women are asymptomatic with no history of bleeding.
- Women have no history of TP prior to pregnancy.
- Plat count usually returns to normal within 2-12 weeks following delivery.
- There is an extremely low risk of fetal or neonatal thrombocytopenia.

■ The mother of our baby-sample had many features of gestational TP such as:
- Her past medical history was free of any bleeding disorders.
- No history of TP during her first pregnancy, and first baby was a healthy girl without any signs of bleeding.
- Also, her plat returned to normal after delivery.

■ Why was the second baby severely affected??

■ Was it because of iso-immune TP "allo_ immune"??

■ There were few features in her medical history against iso-immune TP:
- Firstly, her plat count was low during pregnancy " a mother with iso-immune TP usually have normal plat count".

- Secondly, her first baby was unaffected "in maternal iso-immune TP, the first born baby is usually affected in about half of cases". Also, TP is often severe and occurs earlier with each successive pregnancy.
- Fetal TP recurs in 70% - 90% of subsequent pregnancies.

◙ **Was it maternal ITP which caused the baby bleeding problems??**

Few feature against maternal ITP:

- Prior to pregnancy, no history of ITP.
- No history of splenectomy and normal maternal plat count after delivery.
- Her first baby was normal at birth.

■ Because we lacked facilities at our hospital, we could not check the mother plat antibodies and zygozity of the father.

■ Iso-immune TP has an incidence of 1: 1500, "6-7-8". The mother plat count is normal and the babies are usually well and healthy, present with petechiae and low plat count.

■ The pathogenesis of iso_immune TP is similar to Rh- haemolytic disease of the newborn.

■ The fetus plat carries on an antigen:

- The HPA_1a and HPA_5b or PL_a1, which are similar to the antigens on the father plat, are not on the mother's plat, "PLA 1-negative".

■ 98% of the population are PLA1- positive.

■ The mother produces antibodies against the fetal plat "the newborn is the primary target" and leads to fetal and neonatal thrombocytopenia.

■ The disease varies in severity from mild to moderate resolving in the first week of life without clinical sequlae to extensive fetal or neonatal ICH, leading to death or long term neurodevelopment sequelae.[9-13]

■ In untreated cases, ICH occurs in about 10% of cases with long term neurodevelopmental sequelae in 20% of the survivors.[6-7]

■ Unlike Rh_disease, severe iso immune TP occurs during the first pregnancy in 40_50% of cases.

■ The diagnosis depends on demonstrating plat antigen incompatibility between mother, fetus and baby. In up to 10% of cases antibodies to the plat are undetectable during pregnancy and can only be found after delivery.[6-15]

■ Severe TP and ICH in babies born to mothers with history of auto- immune TP are rare and milder than babies who are born to mothers with history of iso_immune TP.

■ The affected babies of mothers with ITP are generally well appearing, do not have hepatosplenomegaly and have TP that persists for 3-12 weeks postnatally.

■ The antiplatelet antibodies are against maternal and fetal plat and the baby is the secondary target, so both the mother and the baby have low plat count.

■ In iso_immune TP, the mother plat count is normal but the baby plat count is low.

■ Mothers who have been splenectomized may still produce auto- antibodies.

■ Mother who have iso_immune TP, the risk of her baby can be prevented by fetal blood sampling for PLA typing at 20-22 week with repeated procedure at 37-38 week, with weekly or twice weekly IV transfusion PLA -negative plat.

■ From the late second trimester and delivery once fetal lung maturity is attained, the alternative treatment is weekly; administration of high dose of immunoglobulin to the mother.

Conculsion:

◙ The management of our unlucky baby was not up to the standard for many reasons such as:

- Poor recording of the patient medical history.
- Communication between the obstetrician and the neonatologist was missing.

◙ Hopefully, our physician and obstetrician will look carefully after:

- The mother, if she gets pregnant again, and to inform the neonatal team before she goes to work.

◙ Certainly, this is the only way to prevent and minimize the risks to her newborn baby.

◙ The hospital should provide enough supply of immunoglobulin and blood products all the time.

TP\ thrombocytopenia

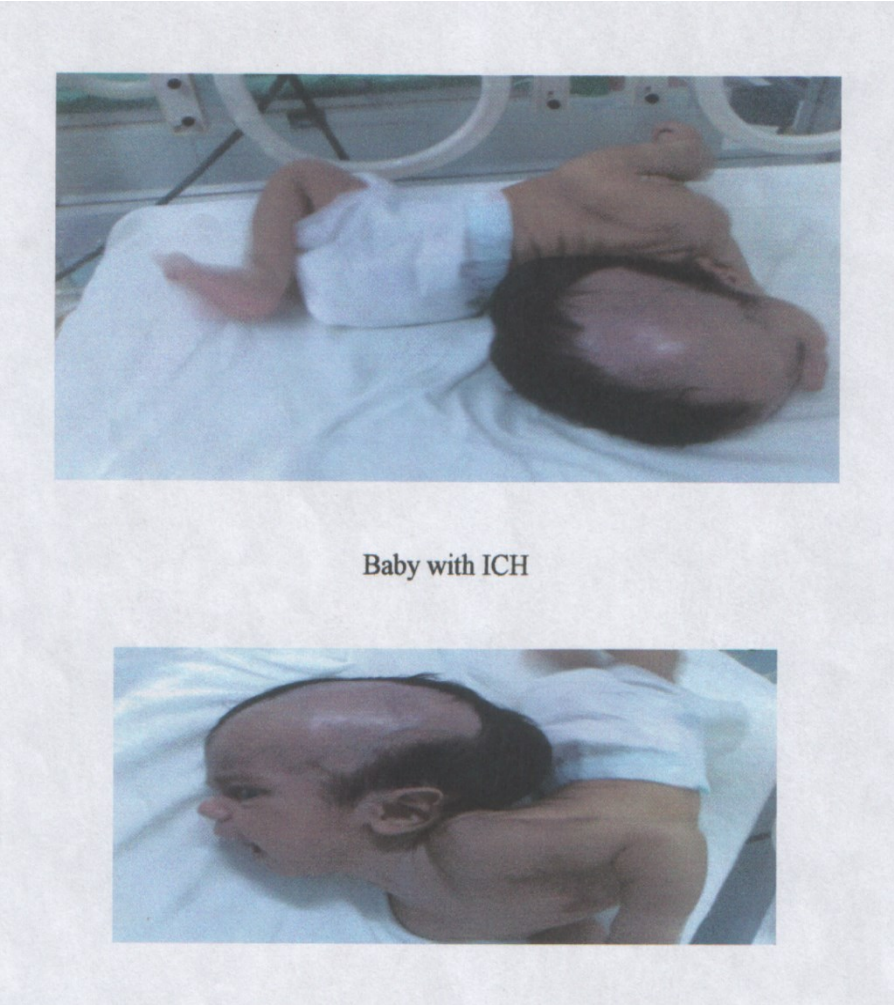

Fig. 1: Baby with ICH.

References:

1. Pahal G, Jauniaux E. Kinnon C,et al. Normal development of human fetal hematopoiesis between eight & seventeen weeks gestation.Am J Obstet Gynecol 2000;183: 1029-34.
2. Holmberg L, Gustavii B. Jonsson A. A prenatal study of fetal platelet count & size with application to the fetus at risk of Wiskott Aldrich syndrome. J pediatr, 1983: 102:773-81.
3. Forestier F. Daffos F. Galacteros F. Haematological value of 163 normal fetus between 18 & 30 weeks of gestation. Peditr Res, 1986; 20: 342-6.
4. Forestier F. Daffos F.Catherine N, et al. Developmental hematopoiesis in normal human fetal blood. Blood 1991; 77:2360-3.
5. Hohlfeld P. Forestier F, Kaplan C, et al. Fetal thrombocytopenia: a retrospective survey of 5,194 fetal blood sampling. Blood 1994; 84: 1851-6.
6. Burrows RF, Kelton JG.. Incidentally detected thrombocytopenia in healthy mothers & their infants. N Engi J Med 1988; 319: 142-5.
7. Sainio S, Jarvenpaa A-S, Renlund M. et al. Thrombocytopenia in term infant: a population-based study. Obstet Gynecol, 2000; 95 : 441-6.
8. demoerloose P, Boehlen F. Extermann P. et al. Neonatal thrombocytopenia: incidence & characterization of maternal antiplatelet antibodies by MAIPA assay. Br Haematol, 1998 ;100:735-40.
9. Burrows RF, Kelton JG. Fetal thrombo-cytopenia & its relation to maternal thrombocytopenia. N Englj Med 1993: 329: 1463-6.

10. Uhrynowska M, Niznikowska-Marks M, Zupanska B. Neonatal & maternal thrombocytopenia: incidence &immune background. Eur J Haematol 2000; 64:42-6.
11. Dreyfus M, Kaplan C. Verdy E, et al. Frequency of immune thrombocytopenia in newborn: a prospective study. Immune thrombocytopenia working group. Blood, 1997: 89: 4402-6.
12. Castle V. Andrew M, Kelton J, et al. Frequency & mechanism of neonatal thrombocytopenia. J Pediatr, 1986:108: 749-55.
13. Mehta P, Rohitkumar V, Neumann L. et al. Thrombocytopenia in the high-risk infant. J Pediatr, 1980;97:791-4.
14. Murray NA, Roberts IAG. Circulating megakaryocyte & their progenitors in early thrombocytopenia in preterm neonate. Pediatr Res 1996;40:112-19.
15. Murray NA Jiowarth U,McCloy MP, et al. Platelet transfusion in the management of severe thrombocytopenia in neonatal ICU patients. Transfus Med, 2002;12: 35-41.
16. Kelton JG, Idiopathic thrombocytopenia purpura complicating pregnancy. Blood Rev, 2002;16:43-6.
17. Burrows RF, Kelton JG. Thrombocytopenia during pregnancy. In Greer IA, Forner CD"eds". Haemostasis & thrombosis in obstetrics & gynecology, London: Chapman & Hall,1992; pp. 407-429.
18. Murray JM. Harris RE. The management of pregnant patient with idiopathic thrombocytopenic purpura, AMJ. Obstet. Gynecol, l987;126:449-451.
19. Roberts IA, Murray NA. Neonatal thrombocytopenia: new insights into pathogenesis & implications for clinical management Curr Opin pediatr, 2001;13:16-21.
20. Blanchette VS, Johnson J, Rand M. The managment of allo-immune neonatal thrombocytopenia. Baillieres Best Pract Res. Clin. Haematol, 2000;13:365-90.
21. Dreyfus M, Kaplan C. Verdy E. Frequency of immune thrombocytopenia in newborn: a prospective study. Blood, 1997; 89:4402-6.
22. De Vries LS,Connell J, Bydder GM, et al. Recurrent ICH. in utero in an infant with allo-immune thrombocytopenia. Br. J obtet. Gynecol, l988;95:299-302.
23. Ouwehand WH, Smith G, Ranasinghe E. Management of sever allo-immune thrombocytopenia in the newborn. Arch Dis Child Fetal Neonatal Ed, 2000;82:fl37-5.
24. Kaplan C. Alloimmune thrombocytopenia of fetus & newborn. Blood Rev, 2002;16: 69-72.
25. Rothenberger S. Neonatal alloimmune thrombocytopenia.Ther Apher, 2002; 6:32-5.
26. Jolly MC, Letsky EA, Fisk NM. The management of fetal alloimmune thrombocytopenia. Prenat diagn, 2002;22:96-8.
27. Bussel JB. Alloimmune thrombocytopenia in the fetus & newborn, semin thromb hemost, 2001;27:245-52.
28. Murphy MF, Waters AH, Doughty HA, et al. Antenatal management of fetomaternal alloimmune thrombocytopenia: report of 15 affected pregnancies. tranfus Med, 1994; 4: 281-92.
29. Kaplan C, Murphy MF, Kroll H. et al, Feto-maternal alloimmune thrombocytopenia: antenatal therapy with IV ig G & steroid; more questions than answers. European working group on FMAIT. Br J Haematol, 1998;100:62-5.