

PREGNANCY AND PREGNANCY OUTCOME IN A PATIENT WITH IDIOPATHIC THROMBOCYTOPENIC PURPURA

Nikolay Kolev

Medical University – Varna, MBAL “St. Anna” AD – Varna, Bulgaria, domkolevi@abv.bg

Nikoleta Tabakova

Medical University – Varna, Specialized Hospital for Obstetrics and Gynecology “Prof. Dimitar Stamatov” – Varna, Bulgaria, Nikoleta8708@gmail.com

Maria Marinova

Resident at Specialized Hospital for Obstetrics and Gynecology “Prof. Dimitar Stamatov” – Varna, Bulgaria, mimionchik@gmail.com

Abstract: Idiopathic thrombocytopenic purpura, otherwise known as primary immune thrombocytopenia, is an immune-mediated acquired disease that presents with decreased platelet count and associated risk of bleeding. In most cases there are autoimmune antibodies involved in the pathophysiology of the disease. Thrombocytopenia is found during laboratory testing and is defined as platelet count less than 150 000 per microliter per blood whereas higher risk of bleeding complications occurs usually at counts less than $50 \times 10^9 /L$. In most cases patients stay asymptomatic and the low platelet count is an accidental finding. Furthermore, it is well known that pregnancy is a prothrombotic state and it is hence more likely for thrombocytopenia to stay unrecognized. Most common diagnoses presenting with thrombocytopenia during pregnancy are gestational thrombocytopenia, hypertensive disorders, and immune processes. Case presentation: A thirty-eight-year-old primipara at thirty-three gestational weeks was admitted to Obstetrics Department of MBAL “St. Anna” AD – Varna with diagnosis “Foetus mortus”, blood pressure of 180/100 mmHg, heartbeat of 70 bpm, last menstrual period on 26.01.2018 and estimated delivery date on 02.11.2018. She was previously diagnosed with idiopathic thrombocytopenic purpura. From anamnesis – a pregnant woman with abdominal pain and uterine contractions on tocolytic and spasmolytic therapy showing no significant effect on pain syndrome and shortened cervical length of 25 mm measured with transvaginal ultrasound. She was previously hospitalized once to Department of pathological pregnancy in SBAGAL – Varna. On physical examination she showed hemorrhagic rash on extremities with eyelid, lower leg, and ankle edema. From observation – centripetal type of fat distribution. From laboratory - : Hemoglobin 131g/L; Hematocrit 0,405 L/L; Erythrocytes 4,66 T/L; Leukocytes 17,80 G/L; Platelets $22 \times 10^9/L$; Fibrinogen 4,61 g/L; Total proteins 60 g/L; Urea 2,8 mmol/l; ASAT – 26,4 U/I; ALAT 33,0 U/I; Blood glucose – 5,4 mmol/L; Bleeding time – 150 sec; Blood clotting time – 420 sec. Induction of labour with 10 IU/ml oxytocin in 500 ml 0,9% NaCl solution was initiated by reason of the unfavourable cervical score. Magnesium tocolysis and antihypertensive drug chlorthalidone were also included in the plan of action due to the high blood pressure. On the 16th hour from induction of labour a non-vital macerated fetus with sign of Spalding was delivered. Episiotomy was not performed due to the higher risk of bleeding. During the third stage of labour total blood loss accounted for 150-200 ml. Conclusion: Despite the advances in medical sciences, immune thrombocytopenia could have a significant impact on both fetal and maternal life and there is always a chance of unfavourable progression of the disorder.

Keywords: ITP, thrombocytopenia, immune thrombocytopenia, pregnancy, purpura

1. INTRODUCTION

Idiopathic thrombocytopenic purpura (ITP) is an immune-mediated acquired disease characterized by low platelet count and an increased risk of bleeding (Cooper & Bussel, 2006). Based on the etiology and pathogenesis there are various terms to refer to that condition – immune thrombocytopenic purpura; immune thrombocytopenia (by reason of the prevalence of asymptomatic cases); etc, so now the condition is more preferred to be classified as primary immune thrombocytopenia (Rodeghiero et al, 2009).

Primary or idiopathic thrombocytopenia is a diagnosis of exclusion and there is no clear underlying cause of the condition (Neunert et al, 2011; Provan et al, 2019), whereas in secondary thrombocytopenia – it is induced by other diseases (infectious, autoimmune, lymphoproliferative, etc), transfusions, vaccines, or drugs (Douglas et al, 2009). The pathophysiology of ITP is connected with the production of autoantibodies that are mostly IgG and most frequently target platelet membrane glycoproteins IIb-IIIa and Ib-IX followed by opsonization, phagocytosis and destruction (Van Leeuwen et al 1982; McMillan et al 1987; Schwartz, 2007). Anti-GPIIb-IIIa antibodies require $Fc\gamma$ receptor ($Fc\gamma R$) for the destruction of platelets while anti-GPIb-IX antibodies follow an $Fc\gamma R$ - independent pathway for desialylation of platelets (Li et al, 2015). Loss of sialic acid in platelets is connected with their removal from the

blood circulation, triggered production of thrombopoietin and therefore megakaryocyte proliferation (Grozovsky et al, 2015). Sialidase is said to reverse this cascade (Marini et al, 2021). Higher rates of platelet desialylation are associated with lower platelet count and poor response to common therapies (Tao et al, 2017; Revilla et al, 2019; Marini et al, 2021). For the help of determining ITP among patients above the age of 60 or those showing a robust response to treatment a bone marrow biopsy could be performed additionally, where increased megakaryocyte production may be present (Cines & Bussel, 2005).

Thrombocytopenia, platelet count below $150\,000 \times 10^9/L$, is the second most common hematologic abnormality found among pregnant women (Sullivan et Martin, 1995). Counts lower than $100\,000 \times 10^9/L$ are encountered in approximately 1% of women during pregnancy (Gernsheimer, James et Stasi, 2013). The most common causes of thrombocytopenia during pregnancy are the following - gestational thrombocytopenia (75%); hypertensive disorders (15-20%); immune processes (3-4%); infections; malignancies etc (Burrows & Kelton, 1990). However, pregnant women with low platelet count usually show less symptoms due to the procoagulant state induced by pregnancy itself (Calderwood, 2006).

Despite the fact most individuals stay asymptomatic, very low platelet count could lead to bleeding diathesis and purpura (Cines & Bussel, 2005). Risk of posttraumatic bleeding increases at platelet counts below $50\,000 \times 10^9/L$; petechia and purpura usually can develop at platelet counts below $20\,000 \times 10^9/L$; and if they are less than $10\,000 \times 10^9/L$ severe bleeding could emerge. (Cines & Bussel, 2005; Kayal, Jayachandran & Singh, 2014). Haemorrhage during labour following a vaginal delivery is not usual maternal concern even with very low platelet count, although postpartal complications are possible due to the fall in pro-coagulant factors (Webert et al, 2003). For providing anaesthesia two and half decades ago the recommended threshold used to be $50 \times 10^9/L$ (Letsky and Greaves, 1996) whereas approximately 15 years later a threshold of $75 \times 10^9/L$ (Provan et al, 2010) and $80 \times 10^9/L$ were recommended if no other comorbidities or risk factors are present (van Veen et al, 2010). For patients that are at risk of bleeding with platelet counts lower than $20\,000 \times 10^9/L$ or show bleeding symptoms treatment is indicated, while asymptomatic patients with mild thrombocytopenia can be observed (Cines & Bussel, 2005).

Case presentation: A 38-year-old primipara, LMP – 26.01.2018, EDD – 02.11.2018, arrived for the first time in the Obstetrics Department of MBAL “St. Anna” AD- Varna with admitting diagnosis “Foetus mortus”, thirty-three gestational weeks, a blood pressure of 180/100 mmHg, and a heart rate of 70 bpm.

Anamnesis: Pregnant woman with abdominal pain and uterine contractions on tocolytic therapy with magnesium and spasmolytic drugs, showing no significant effect on pain syndrome, shortened cervical length of 25 mm measured with transvaginal ultrasound (TVUS). The patient was previously hospitalized once to Department of pathological pregnancy in SBAGAL – Varna.



Fig. 1. Eyelid edema and thrombocytopenic purpura on extremities

Physical examination: Hemorrhagic rash on extremities; eyelid, lower leg, and ankle edema (Fig 1); a blood pressure of 180/100 mmHg; a heart rate of 70 bpm. From observation- centripetal type of fat distribution- fat deposition in the regions of shoulders, chest, and abdomen while extremities and pelvis remain relatively low-fat.

Laboratory investigations: Hemoglobin 131g/L; Hematocrit 0,405 L/L; Erythrocytes 4,66 T/L; Leucocytes 17,80 G/L; Platelets 22×10^9 ; Fibrinogen 4,61 g/L; Total proteins 60 g/L; Urea 2,8 mmol/l; ASAT – 26,4 U/I; ALAT 33,0 U/I; Blood glucose – 5,4 mmol/L; Bleeding time – 150 sec; Blood clotting time – 420 sec.

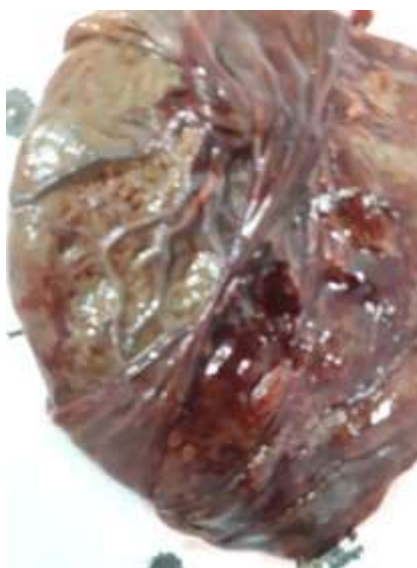
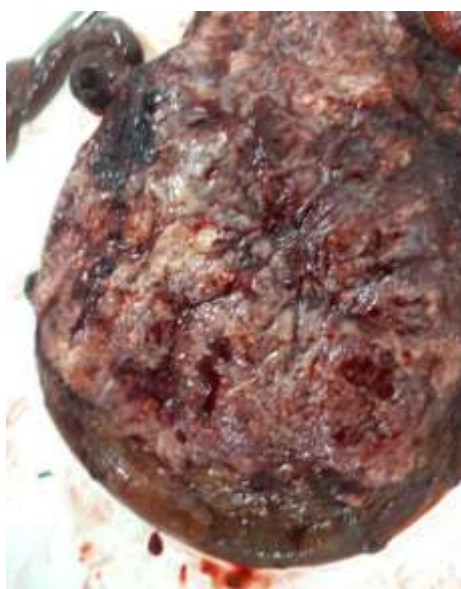
Fig. 2. Spalding sign



Fig. 3. Male macerated fetus



Fig. 4. Placenta showing multiple infarctions



Absence of fetal heart beats and no fetal movements were reported upon admission in Obstetrics Department of MBAL “St. Anna”- Varna. Due to unfavourable cervical score labour induction was initiated with the use of Oxytocin 10 IU/ml in 500 ml 0,9% NaCl solution intravenously. Since blood pressure values of the patient were high, Magnesium tocolysis treatment and antihypertensive drug Chlophazolin were also included in the plan of action. On the 16th hour from onset of induction of labour a male non-vital macerated fetus with Spalding sign (Fig. 2.) weighing 1550 g and 41 cm tall was expelled (Fig. 3.). The delivered placenta weighted 300 g and the umbilical cord was 45 cm long (Fig.4.). Total amount of blood loss during the third stage of labour was 150-200 ml. During the second stage of labour episiotomy was not performed due to high risk of bleeding.

Conclusion: ITP could be a serious medical condition with impact on both maternal and fetal life, and despite the advances in medical sciences, there is always a chance for unfavourable progression of the disorder.

REFERENCES

Burrows, R. F., & Kelton, J. G. (1990). Thrombocytopenia at delivery: a prospective survey of 6715 deliveries. American journal of obstetrics and gynecology, 162(3), 731-734.

- Calderwood, C. J. (2006). Thromboembolism and thrombophilia in pregnancy. *Current Obstetrics & Gynaecology*, 16(6), 321-326.
- Cines, D. B., & Bussel, J. B. (2005). How I treat idiopathic thrombocytopenic purpura (ITP). *Blood*, 106(7), 2244–2251. <https://doi.org/10.1182/blood-2004-12-4598>
- Cooper, N., & Bussel, J. (2006). The pathogenesis of immune thrombocytopaenic purpura. *British journal of haematology*, 133(4), 364–374. <https://doi.org/10.1111/j.1365-2141.2006.06024.x>
- Douglas B. Cines, James B. Bussel, Howard A. Liebman, Eline T. Luning Prak (2009); The ITP syndrome: pathogenic and clinical diversity. *Blood*; 113 (26): 6511–6521. doi: <https://doi.org/10.1182/blood-2009-01-129155>
- Grozovsky, R., Begonja, A. J., Liu, K., Visner, G., Hartwig, J. H., Falet, H., & Hoffmeister, K. M. (2015). The Ashwell-Morell receptor regulates hepatic thrombopoietin production via JAK2-STAT3 signaling. *Nature medicine*, 21(1), 47–54. <https://doi.org/10.1038/nm.3770>
- Kayal, L., Jayachandran, S., & Singh, K. (2014). Idiopathic thrombocytopenic purpura. *Contemporary clinical dentistry*, 5(3), 410–414. <https://doi.org/10.4103/0976-237X.137976>
- Li, J., van der Wal, D. E., Zhu, G., Xu, M., Youbare, I., Ma, L., Vadasz, B., Carrim, N., Grozovsky, R., Ruan, M., Zhu, L., Zeng, Q., Tao, L., Zhai, Z. M., Peng, J., Hou, M., Leytin, V., Freedman, J., Hoffmeister, K. M., & Ni, H. (2015). Desialylation is a mechanism of Fc-independent platelet clearance and a therapeutic target in immune thrombocytopenia. *Nature communications*, 6, 7737. <https://doi.org/10.1038/ncomms8737>
- Marini, I., Zlamal, J., Faul, C., Holzer, U., Hammer, S., Pelzl, L., Bethge, W., Althaus, K., & Bakchoul, T. (2021). Autoantibody-mediated desialylation impairs human thrombopoiesis and platelet lifespan. *Haematologica*, 106(1), 196–207. <https://doi.org/10.3324/haematol.2019.236117>
- McMillan, R., Tani, P., Millard, F., Berchtold, P., Renshaw, L., & Woods, V. J. (1987). Platelet-associated and plasma anti-glycoprotein autoantibodies in chronic ITP.
- Neunert, C., Lim, W., Crowther, M., Cohen, A., Solberg, L., Jr, Crowther, M. A., & American Society of Hematology (2011). The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood*, 117(16), 4190–4207. <https://doi.org/10.1182/blood-2010-08-302984>
- Provan, D., Arnold, D. M., Bussel, J. B., Chong, B. H., Cooper, N., Gernsheimer, T., Ghanima, W., Godeau, B., González-López, T. J., Grainger, J., Hou, M., Kruse, C., McDonald, V., Michel, M., Newland, A. C., Pavord, S., Rodeghiero, F., Scully, M., Tomiyama, Y., Wong, R. S., ... Kuter, D. J. (2019). Updated international consensus report on the investigation and management of primary immune thrombocytopenia. *Blood advances*, 3(22), 3780–3817. <https://doi.org/10.1182/bloodadvances.2019000812>
- Revilla, N., Corral, J., Miñano, A., Mingot-Castellano, M. E., Campos, R. M., Velasco, F., Gonzalez, N., Galvez, E., Berruete, R., Fuentes, I., Gonzalez-Lopez, T. J., de la Morena-Barrio, M. E., Gonzalez-Porras, J. R., Vicente, V., & Lozano, M. L. (2019). Multirefractory primary immune thrombocytopenia; targeting the decreased sialic acid content. *Platelets*, 30(6), 743–751. <https://doi.org/10.1080/09537104.2018.1513476>
- Rodeghiero, F., Stasi, R., Gernsheimer, T., Michel, M., Provan, D., Arnold, D. M., Bussel, J. B., Cines, D. B., Chong, B. H., Cooper, N., Godeau, B., Lechner, K., Mazzucconi, M. G., McMillan, R., Sanz, M. A., Imbach, P., Blanchette, V., Kühne, T., Ruggeri, M., & George, J. N. (2009). Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood*, 113(11), 2386–2393. <https://doi.org/10.1182/blood-2008-07-162503>
- Schwartz R. S. (2007). Immune thrombocytopenic purpura--from agony to agonist. *The New England journal of medicine*, 357(22), 2299–2301. <https://doi.org/10.1056/NEJMe0707126>
- Tao, L., Zeng, Q., Li, J., Xu, M., Wang, J., Pan, Y., Wang, H., Tao, Q., Chen, Y., Peng, J., Hou, M., Jansen, A. J., Ni, H., & Zhai, Z. (2017). Platelet desialylation correlates with efficacy of first-line therapies for immune thrombocytopenia. *Journal of hematology & oncology*, 10(1), 46. <https://doi.org/10.1186/s13045-017-0413-3>
- Van Leeuwen, E. F., Van Der Ven, J. T., Engelfriet, C. P., & Von Dem Borne, A. E. (1982). Specificity of autoantibodies in autoimmune thrombocytopenia.
- Webert, K. E., Mittal, R., Sigouin, C., Heddle, N. M., & Kelton, J. G. (2003). A retrospective 11-year analysis of obstetric patients with idiopathic thrombocytopenic purpura. *Blood*, 102(13), 4306–4311. <https://doi.org/10.1182/blood-2002-10-3317>