Fetal and neonatal alloimmune thrombocytopenia is a disease caused by maternal production of an antibody-mediated immunological response against a platelet-specific antigen, present on the fetal platelets and inherited from the father. Maternal IgG alloantibodies form antigen-antibody complex that lead to fetal platelet destruction. There are several human platelet antigens that play crucial role in FNAT pathogenesis, from which HPA-1a and HPA-5b are the most frequent. The incidence ranges from 1:1000 to 1:2000 and main diagnostic criteria is platelet count lower than 150×10⁹/L. The mother was found to be HPA-1a negative, the child was HPA-1a positive and the diagnosis of FNAT was confirmed by maternal HPA-1a alloantibodies. The father was homozygous positive HPA-1a/a.

Today, in most clinical centers, intravenous immunoglobulins (IVIG) are the first-line therapy, but therapeutic protocols regarding dosage and duration are not yet established and confirmed. There is a lack of controlled randomised trials due to the low incidence of FNAT. Therapeutic protocols are mostly derived from case reports and small series. In this report, we present a successful treatment of FNAT in secundipara who delivered in her first pregnancy newborn with a heavy form of neonatal autoimmune thrombocytopenia.
Discussion

Fetal and neonatal alloimmune thrombocytopenia is mainly diagnosed in pregnant women who had given birth to an affected child. Diagnosis is rarely made in the first pregnancy when intra or extracranial hemorrhage is detected on ultrasound or there is anamnestic data about FNAT in sisters or close family members. Nevertheless, in most Western countries apart from Norway and Denmark, the FNAT screening program is not implemented because of high cost and low incidence of the disease. In our case, the outcome of the first pregnancy was an indication for the FNAT testing and the diagnosis was confirmed by maternal antiplatelet HPA-1a antibodies and paternal HPA-1a/a homozygosity. If the father is heterozygous HPA-1a/b then there is a 50% chance that the fetus is HPA-1bb. In that case, amniocentesis is indicated for fetal genotype testing. If the fetal genotype is HPA-1bb, the condition can be excluded because it is identical to the mother’s genotype. Some countries have recently implemented HPA typing of free fetal DNA isolated from maternal blood.

About thirty years ago FNAT was exclusively treated by intrauterine platelet transfusions (IPT). The lack of such therapeutic approach is weekly repetitions due to short half-life of transfused platelets and severe complications like bradycardia, prolonged insertion bleeding or cord thrombosis. The risk of fetal loss or an emergency premature Caesarean section after IPT is 11%. Bussel and al. introduced IVIG to achieve the same therapeutic effect and to avoid procedure-related complications. Therapy is being implemented based on reports of beneficial effects of maternal administration of IVIG in pregnancies with immune thrombocytopenia. The basic principle of IVIG treatment is prevention of thrombocytopenia-related bleeding complications, however, the working mechanism of IVIG is still not clear and remains subject of research. Most likely, it acts on various levels, most important of which are the stabilisation of blood vessels endothelium and the interference HPA antibody transduction. If there is no treatment, risk of fetal bleeding in index pregnancy in women with previous fetal ICH is 79%. Over the last two decades IVIG therapy has almost completely replaced the IPT with a nearly 100% success rate of fetal bleeding prevention. Some authors combine IVIG therapy with steroids, however, randomised studies reported no significant difference on fetal loss, ICH frequency or neonatal platelet count. Dosage of IVIG and length of therapy is based on anamnestic data of ICH in the previous pregnancy. Generally, high-risk pregnancies should be treated with higher dose of IVIG and an earlier onset of IVIG administration compared to low-risk pregnancies.

There is no consensus regarding the doses and length of IVIG treatment. The recommendations are different and doses vary from 0.5 to 2.0 g/kg of the mother’s body weight/per week. The Dutch group recently recommended weekly doses of IVIG of 1.0 g/kg for high-risk pregnancies started from 12th to 16th week and continued until the 36th week when delivery should be planned. For low-risk pregnancies weekly doses of IVIG consist of 0.5 g/kg from 24 to 37 weeks. In both cases, ultrasound exam of fetal brain should be performed every two to four weeks. Winkelhorst et al. draw attention to the risk of extracranial hemorrhage during pregnancy and authors described gastrointestinal bleeding, as well as bleeding in spinal canal, lungs, kidneys, eyes etc. Norwegian authors indicate and moderate therapy according to the maternal anti-HPA 1a antibody level. They reported the sensitivity of over 90% in predicting severe neonatal thrombocytopenia. This concept does not apply in other countries with arguing that the level and dynamics of the antibody does not correlate to the severity of FNAT. Moreover, cases with severe fetal bleeding and minimal maternal anti-HPA-1a antibody concentrations have been reported.

In this case, we considered that there was a high risk of hemorrhage due to severe thrombocytopenia and extensive petechial bleeding in the sibling. Therefore, the doses of IVIG and length of therapy have been applied for a high-risk pregnancy. The therapy strategy was not changed due to normal ultrasound findings of the fetus and mother’s favorable tolerance to the medication. Although the level of HPA-1a antibodies are not reliable for the monitoring the therapeutic effect, we concluded that the titre drop from 1:64 in the 10th week at 1:16 in the 29th week indirectly indicated a good therapeutic effect. This finding correlated with the umbilical cord platelets count (146×10^9/L) after birth and negative findings of a direct test of antiplatelet IgG antibodies and antiplatelet antibodies determined by the immuno-fluorescence method. There is no consensus of how to deliver pregnant women with FNAT, although smaller cohort studies have not shown that vaginal delivery increases the risk of ICH. In low-risk cases, vaginal delivery is preferred around the 38th week. Due to risk of fetal bleeding, any trauma such as assisted delivery the use of a scalp electrode or collecting blood from the fetus should be avoided during delivery. Most centers recommend Cesarean section between the 36th and 38th weeks of gestation, if there was ICH in the previous pregnancy. Some centers use cordocentesies to verify therapeutic effect and to choose the mode of delivery. In our case Cesarean section was performed because the mother did not accept any risk of vaginal delivery even with the risk of possible cordocentesies. According to the platelet count from umbilical cord after delivery (146×10^9/L) it can be concluded that birth could have been performed vaginally.

A study that analyzed the period from 2009 to 2013 has revealed that 52 newborns in Croatia were diagnosed with FNAT. The analysis was possible for 38 newborns and the results showed that none of newborns had ICH. No symptoms showed 20 newborns (53%), 16
had petechiae (42%) and 2 had gastrointestinal bleeding (5%). The average platelet count was 50×10^9/L (min 5, max 107). The treatment was not required for 29 newborns (76%) and others were treated with platelet transfusions, immunoglobulins and corticosteroids. According to the total number of births in Croatia in that period the incidence of FNAT is 1:4000 births. By exploring Croatian medical data, we have not been able to access the data on the numbers and treatment methods of pregnant women with FNAT in the previous pregnancy.

In this case, since there were no clinical or laboratory findings of FNAT in the newborn it can be concluded that prenatal therapy was successful. Normal neonatal platelet count and non-detectable antiplatelet IgG antibodies indicate that the duration of therapy and therapy doses were optimal.

Submission declaration

We hereby confirm that the manuscript has no any actual or potential conflict of interest with any parties, including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence or be perceived to influence. We confirm that the paper has not been published previously, it is not under consideration for publication elsewhere, and the manuscript is not being simultaneously submitted elsewhere.”

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DIJAGNOZA FETONEONATALNE ALOIMUNE TROMBOCITOPENIJE I USPJEŠNO LIJEČENJE INTRAVENSKIM IMUNOGLOBULINIMA

Miljenka Lemac, Berivoj Mišković

Kljucne riječi: fetalna i neonatalna aloimuna trombocitopenija, antitrombocitna antitijela, HPA-1a, intravenski imunoglobulini

Sažetak. U prikazu slučaja je opisan dijagnostički postupak i uspješno liječenje fetoneonatalne aloimune trombocitopenije (FNAT) kod trudnice koja je u prethodnoj trudnici rodila dijete sa teškim oblikom ove bolesti. Dijagnoza FNAT postavljena je postnatalno dokazom anti-HPA-1a antitrombocitnih protutijela kod HPA-1a negativne majke i oca koji je bio HPA-1a/a pozitivan homozigot. Novorođeni je zbog izraženih petehijalnih krvarenja i teške trombocitopenije (19 × 10^9/L) liječen transferzijama trombocita i kortikosteroidima. U ovoj trudnici je, s obzirom na ishod prethodne trudnici, indicirano liječenje intravenskim imunoglobulini (IVIG). Liječenje je trajalo od 20. do 35. tjedna jedanput tjedno u dozi 1 g/kg tjelesne težine majke. Trudnica je protekla bez fetalnih i majčinskih komplikacija, a elektivnim carskim rekom je 36. tjedna porođeno žensko vitalno dijete 3720 g. Izostanka kliničkih simptoma FNAT te uredan nalaz trombocita iz pupkovine (146 × 10^9/L) i negativan direkti test na antitrombocitna protutijela IgG i imunofluorescentna antitrombocitna protutijela ukazuju na optimalan terapijski učinak s IVIG. S obzirom da FNAT u dijagnostičkom i terapijskom smislu ne spada u kliničku rutinu korisno je objavljivanje i prikupljanje pojedinačnih slučajeva ove rijetke bolesti.