RESEARCH ARTICLE

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Management of Primary Immune Thrombocytopenia: Turkish Modified Delphi-Based Consensus Statement for Special Considerations

Primer İmmün Trombositopeni Yönetimi: Özel Durumlar için Düzenlenmiş Türkiye Delphi Temelli Konsensus Bildirisi

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Abstract

Objective: Primary immune thrombocytopenia (ITP) is an acquired disorder of platelets with a complex and unclear mechanism of increased immune destruction or impaired production of platelets. While the management of ITP is evolving, there is still a need for guidance, particularly in certain circumstances such as pregnancy, emergencies, or patients requiring co-medications. We aimed to determine the tendencies of hematologists in Türkiye in the event of such special considerations.

Materials and Methods: Applying a modified Delphi method, the Turkish National ITP Working Group, founded under the auspices of the Turkish Society of Hematology, developed a questionnaire consisting of statements regarding pregnancy, emergencies, and circumstances requiring co-treatment with antiaggregants or anticoagulants. A total of 107 hematologists working in university or state hospitals voted for their agreement or disagreement with the statements for two sequential rounds.

Öz

Amaç: Primer immün trombositopeni (ITP), trombositlerin karmaşık ve tam aydınlanmamış bir mekanizma ile artmış immün yıkım ya da azalmış yapımına bağlı olarak azaldığı edinsel bir hastalıktır. ITP tedavisi gelişmek ile birlikte, gebelik, acil durumlar ve ek tedavi gereksinimi gibi özel durumların yönetimi için rehberlere ihtiyaç vardır. Çalışmamızdaki amaç, Türkiye'deki hematologların bu özel durumlara yaklaşımını belirlemektir.

Gereç ve Yöntemler: Türk Hematoloji Derneği altında kurulan Ulusal ITP Çalışma Grubu tarafından oluşturulan bir anket ile modifiye bir Delphi metodu kullanılarak, gebelik, acil ve ek tedavi gereksiniminde ITP'ye yaklaşım hedeflenmiştir. Üniversite ve devlet hastanelerinde görev yapmakta olan 107 hematoloji uzmanına iki tur halinde bu sorular yöneltilmiştir.

Bulgular: Katılımcı hematologlar, gebelikte trombositin $30x10^9$/L altına inmesi ile tedavi başlanması gerektiği ve $50x10^9$/L üzerindeki değerlerde normal ya da sezaryen doğumun güvenli olacağı

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Abstract

Results: The participating hematologists reached an agreement on starting treatment for pregnant patients with platelets of less than $30x10^9$/L and delivery either vaginally or by cesarean section being safe at platelet counts above $50x10^9$/L. For emergencies and the rescue management of ITP, the panel agreed against the use of high-dose corticosteroids alone, preferring combinations with transfusions or intravenous immunoglobulin. For patients who require interventions, platelet counts of $>50x10^9$/L were regarded as safe for low-risk procedures as well as co-treatment with antiplatelets or anticoagulants.

Conclusion: As the National ITP Study Group, we have observed the need to increase the practice guidance regarding patients with primary ITP requiring additional treatments including invasive interventions and co-treatments for coagulation. Decisions on the management of ITP during pregnancy should be individualized. There is a lack of consensus on the thresholds of platelet counts as well as co-morbidities and co-medications. This lack of consensus may be due to variations in practices.

Keywords: Adult primary immune thrombocytopenia, Management, Delphi method, Special considerations

Öz

konusunda görüş birliğine varmıştır. Acil ve kurtarma tedavilerine ilişkin olarak katılımcıların tek başına yüksek doz kortikosteroidden ziyade transfüzyon ya da intravenöz immünoglobulin ile kombine kullanımını tercih ettikleri gözlenmiştir. Düşük kanama riskli girişimsel işlemler ya da antiagregan veya antikoagulan gibi ek tedavi gereksiniminde $50x10^9$/L üzerindeki trombosit değerlerinin güvenli olabileceği konusunda fikir birliği gözlenmiştir.

Sonuç: Ulusal ITP çalışma grubu olarak girişimsel işlemler ve pıhtılaşma sistemine yönelik ek tedavilerin gerektiği özel durumlarda ITP yönetimine ilişkin uygulama rehberlerine ihtiyaç olduğunu gözlemledik. Gebelikte ITP'nin yönetimine ilişkin kararlar bireyselleştirilmelidir. Trombosit sayısı eşikleri, eşlik eden hastalıklar ve birlikte kullanılan ilaçlar konusunda bir fikir birliği eksikliği vardır. Bu fikir birliği eksikliği klinik pratikteki farklılıklardan kaynaklanıyor olabilir.

Anahtar Sözcükler: Erişkin primer immün trombositopeni, Hastalık yönetimi, Delphi metodu, Özel durumlar

Introduction

Immune thrombocytopenia (ITP) is an acquired disorder of the hemostatic system, formerly regarded as a disease of platelet counts related to increased peripheral destruction but more recently recognized as a type of immune dysfunction, impaired megakaryopoiesis, or a complex interplay resulting in manifestations including bleeding and/or thrombosis [1]. Treatment should be individualized and constructed around the patient's characteristics, including age, co-morbidities and co-medications, and lifestyle. Pregnancy and age-related cardiovascular disorders may be challenges in the management of patients with ITP, and while guidelines have been developed to address these issues, treatment approaches may vary between and within countries due to the availability of agents, economic disparities, and distinctions of practices.

As the National ITP Study Group, we aimed to determine the perspectives of practicing hematologists in Türkiye regarding the management of primary ITP (pITP) during pregnancy, emergency management for patients with bleeding or those requiring surgical interventions, and conditions requiring antiaggregant or anticoagulant co-medication, complementing these perspectives on patient management with international data.

Materials and Methods

The Delphi method is a survey-based form of assessment of perspective. Statements are constructed and presented to the target population, evaluated, and submitted to single or multiple courses of voting until consensus or an adequate impression is obtained. The intended population votes anonymously, selecting their levels of agreement/disagreement. After the outcomes are collected, the statements are appraised by the research team to form a perspective of the target audience [2,3]. Each individual statement is defined and framed based on statements within national and international guidelines by the steering committee.

The National ITP Study Group founded under the auspices of the Turkish Society of Hematology and the Hemostasis and Thrombosis Scientific Subcommittee by hematologists with expertise on ITP constructed a survey consisting of 5 statements addressing pregnancy and 13 statements on emergencies or rescue management and requirements for co-medications. Each individual statement was defined and framed based on statements within national and international guidelines by the steering committee. A total of 107 hematologists of varying ages and facilities agreed to participate in the study, and 88.3% of the participants were under 50 years of age. While 40.2% were working in university hospitals, the remaining 55.8% were working in state hospitals.

The target audience was asked to consider each statement and select a level of agreement using a 5-point Likert-type scale (1: disagree/never, 2: somewhat disagree/rarely, 3: neither disagree nor agree/sometimes, 4: somewhat agree/often, 5: agree/always). The agreement with each statement was expressed as the sum of percentages of votes for "somewhat agree/often" and "agree/always."

Two rounds of voting were conducted with analysis performed halfway through the study to identify statements with a lack of consensus to be submitted for a second round of voting. The second round of voting took place 1 month after the first and the response rates for the rounds were 71.9% and 93.5%, respectively. The results of all assessments are presented here for discussion regardless of the level of agreement.

This study was approved by the local ethics committee (Trakya University Medical School Scientific Ethics Committee: TUTF-BEK 2023/322). All of the participating physicians provided their written informed consent.

Results

Pregnancy and ITP

Statement 1: Pregnant patients with platelet counts of <70x10^9/L should be assessed in terms of ITP.

Agreement: 98%.

Statement 2: Treatment shall be commenced for pregnant patients presenting with platelet counts of <30x10^9/L any time during pregnancy.

Agreement: 92%.

Statement 3: For pregnant patients with ITP, platelet counts of >70x10^9/L are adequate for vaginal delivery.

Agreement: 92%.

Statement 4: For pregnant patients with ITP, platelet counts of >50x10^9/L are adequate for cesarean section.

Agreement: 84%.

Statement 5: For pregnant patients with ITP, platelet counts of >70x10^9/L are adequate for neuraxial anesthesia.

Agreement: 80%.

Emergencies and Rescue Treatment for pITP

Statement 1: Pulse methylprednisolone should be administered in emergency situations requiring rapid platelet recovery.

Agreement: 28%.

Statement 2: High-dose dexamethasone (40 mg/daily, 1-4 days) should be administered in emergency situations requiring rapid platelet recovery.

Agreement: 39%.

Statement 3: High-dose dexamethasone (40 mg/daily, 1-4 days) combined with intravenous immunoglobulin (IVIG) or platelet transfusion should be administered in emergency situations requiring rapid platelet recovery.

Agreement: 73%.

Statement 4: Platelet transfusion can be administered for patients who have IVIG exposure in emergency situations requiring rapid platelet recovery.

Agreement: 40%.

Statement 5: Antifibrinolytics shall be used in emergency situations as supportive treatment.

Agreement: 40%.

Statement 6: For patients who have pITP and are not receiving treatment and will undergo an elective surgical intervention, corticosteroids and IVIG shall be used to increase platelet counts above the safe thresholds.

Agreement: 67%.

Statement 7: For patients who have pITP and are not receiving treatment and will undergo an elective surgical intervention, thrombopoietin receptor antagonists (TPO-RAs) shall be used to increase platelet counts above the safe thresholds.

Agreement: 8%.

Statement 8: For patients with pITP, platelet counts of 30-50x10^9/L are safe for low-risk surgical interventions under adequate local measures.

Agreement: 62%.

Statement 9: For patients with pITP, platelet counts of >50x10^9/L are safe for low-risk surgical interventions under adequate local measures.

Agreement: 94%.

Statement 10: For patients with pITP, platelet counts of >50x10^9/L are safe for antiaggregant treatments.

Agreement: 90%.

Statement 11: For patients with pITP, platelet counts of >50x10^9/L are safe for anticoagulant treatments.

Agreement: 86%.

Statement 12: For patients with pITP, platelet counts of 30-50x10^9/L are safe for antiaggregant treatments.

Agreement: 19%.

Statement: For patients with pITP, platelet counts of 30-50x10^9/L are safe for anticoagulant treatments.

Agreement: 29%.

Discussion

Mild decreases in platelet counts may occur during almost all pregnancies without complications mainly due to increased distribution volume. Thrombocytopenia (<100x10^9/L) is observed in less than 1% of uncomplicated pregnancies [4,5]. Gestational thrombocytopenia is defined as a temporary isolated condition with mild thrombocytopenia (mostly over 100x10^9/L) observed in the late stages without any risk of bleeding or fetal complications and it is the most frequent cause of thrombocytopenia during pregnancy [1,4]. ITP is observed in 1-3/10,000 pregnancies and may occur at any time during pregnancy. The severity of thrombocytopenia is variable and it may fall to levels below 50x10^9/L. Other causes of thrombocytopenia during pregnancy include preeclampsia with severe features, HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, disseminated intravascular coagulation, acute fatty liver of pregnancy, and thrombotic microangiopathies [4,5,6,7]. In our consensus assessment, our panel agreed that for pregnant patients presenting with thrombocytopenia of <70x10^9/L, differential diagnoses including ITP should be investigated, in line with an international consensus report [7].

The management of ITP during pregnancy is largely the same as that for non-pregnant patients, but the goal of treatment is to reduce the risk of bleeding and reach safe platelet counts for delivery rather than normalizing the platelet count. Treatment is not recommended by the American Gynecology and Obstetrics Society for patients who have platelet counts of ≥30x10^9/L without bleeding until 36 weeks of gestation, or until delivery if it commences before that [4]. While a stable platelet count may be pursued, to be on the safe side, our panel agreed that treatment shall be commenced for pregnant patients with platelet counts of <30x10^9/L. This finding may be interpreted as concordant with the relevant consensus report and no thresholds were recommended in the 2011 American Society of Hematology guidelines for starting treatment [6,7]. For patients who have platelet counts of <30x10^9/L or clinically relevant bleeding, oral corticosteroids or IVIG is recommended [1,4]. The oral corticosteroids methyl prednisone and prednisolone are preferred to dexamethasone due to the greater and more rapid placental crossing of dexamethasone [8]. The ideal dose of corticosteroids is not clear and there is no evidence of the superiority of higher doses. Therefore, consensus recommendations have favored daily doses of 0.25-0.5 mg/kg.

Combinations of corticosteroids and IVIG are regarded as second-line treatments, and the safety and use of TPO-RAs in pregnancy have been reported but they are not recommended by international guidelines [6,7]. Since antibodies do not cross the placenta until the second trimester and then increase linearly as the pregnancy advances, rituximab is hypothetically safe during the first trimester. From the attributable data on rituximab used for various indications, the use of rituximab during pregnancy is not clear and thus not recommended [6,7].

Data regarding the use of TPO-RAs during pregnancy are limited and only based on case reports. Decisions on the use of TPO-RAs during pregnancy should be individualized and they cannot be considered routine practice for now. The goal of treatment for patients with ITP during pregnancy is platelets of ≥50x10^9/L at the time of delivery. While data regarding safe platelet counts for neuraxial anesthesia are not available, a 2021 consensus report from the Society for Obstetric Anesthesia stated that platelet counts of >70x10^9/L may be considered as the safe recommendation for avoiding epidural hematoma. The preferences of anesthesiologists may vary within countries and even within centers; therefore, decisions should be made by the multidisciplinary team managing each patient.

In the management of ITP during bleeding or for patients for whom rapid platelet recovery is required, such as in cases of surgical or medical interventions, treatments should be individualized. Contributing factors for these decisions include the severity of bleeding, age, co-morbidities or co-medications that may create an increased tendency for bleeding, the complications of each ITP treatment, and the time that is required or available for platelet increase. Although the bleeding risk is not precisely related to platelet counts, the risk may be regarded as increased when platelet counts are <20x10^9/L [9]. For low-risk procedures such as dental procedures including deep cleaning or simple extraction, counts of ≥30x10^9/L may be adequate, while for complex extractions and minor surgeries, counts of ≥50x10^9/L are to be targeted [7,10]. Our panel agreed that for low-risk procedures, a platelet count of ≥50x10^9/L shall be regarded as adequate, and the lack of agreement on platelet counts between 30x10^9/L and 50x10^9/L may be interpreted as reflecting the need to individualize ITP treatment as well as the risk of interventions being unclear.

Our panel did not reach a consensus on how to manage pITP in cases of bleeding or when rapid recovery is required. The major point that may be regarded as agreement (73% agreement) entailed the combination of high-dose dexamethasone with IVIG or platelet transfusions. While data on the effectiveness of each option in emergency situations are insufficient, the combination of high-dose corticosteroids with IVIG is described as probably effective [7]. Since TPO-RAs require at least 5 days to increase platelet counts, they are not recommended in emergency settings, and our panel did not agree on their use for rescue treatment or rapid platelet recovery [11].

Platelet transfusions with or without IVIG may be considered for patients failing to respond to other treatments and increases of platelet counts of >20x10^9/L may be achieved for almost half of all patients, although the level of evidence is not high. Antifibrinolytics (oral or intravenous tranexamic acid and ε-aminocaproic acid) may be useful to prevent bleeding as a supportive measure, although without any strong evidence. Our panel did not support the use of antifibrinolytics in emergency situations. We have observed a need to increase the awareness and level of education on the management of pITP in acute settings.

Regarding requirements for an antiplatelet or anticoagulant agent, our panel agreed that platelet counts of >50x10^9/L are required. An international consensus report recommended a target level of ≥30-50x10^9/L for a single antiplatelet agent or anticoagulant treatment and ≥50-70x10^9/L for dual antiplatelets or anticoagulants [7]. Patients should be assessed for their individual risk of bleeding, considering factors such as age, sex, bleeding history, fall risk, cancer and cancer treatments, co-medications, and social support, and the target platelet count should be based on this assessment.

Conclusion

Decisions on the management of ITP during pregnancy should be individualized and should be made by multidisciplinary teams including hematologists, obstetricians, and anesthesiologists. We have observed a lack of consensus on the thresholds of platelet counts regarded as safe for interventions as well as co-morbidities and co-medications. This lack of consensus may be due to variations in the practices of the physicians who perform the interventions, as well as the anxiety of hematologists, which may be considered patient- or healthcare system-centered.

Ethics

Ethics Committee Approval: This study was approved by the local ethics committee (Trakya University Medical School Scientific Ethics Committee: TUTF-BEK 2023/322).

Informed Consent: All of the participating physicians provided their written informed consent.

Authorship Contributions

Concept: A.M.D.; Design: A.M.D., E.G.Ü, M.A., M.C.A., M.Ayl., V.K., E.K., F.Ö., N.S., M.S., F.Ş., S.K.T., T.T., İ.Y.; Data Collection or Processing: A.M.D., E.G.Ü, M.A., M.C.A., M.Ayl., V.K., E.K., F.Ö., N.S., M.S., F.Ş., S.K.T., T.T., İ.Y., Ü.Ç.; Analysis or Interpretation: A.M.D., E.G.Ü, M.A., M.C.A., M.Ayl., V.K., E.K., F.Ö., N.S., M.S., F.Ş., S.K.T., T.T., İ.Y.; Literature Search: A.M.D., E.G.Ü, M.A., M.C.A., M.Ayl., V.K., E.K., F.Ö., N.S., M.S., F.Ş., S.K.T., T.T., İ.Y., Ü.Ç.; Writing: A.M.D., E.G.Ü, M.A., M.C.A., M.Ayl., V.K., E.K., F.Ö., N.S., M.S., F.Ş., S.K.T., T.T., İ.Y.

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References

1. Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, Bussel JB, Cines DB, Chong BH, Cooper N, Godeau B, Lechner K, Mazzucconi MG, McMillan R, Sanz MA, Imbach P, Blanchette V, Kühne T, Ruggeri M, George JN. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood. 2009;113:2386-2393.
2. Hsu CC, Sandford BA. The Delphi technique: making sense of consensus. Pract Assess Res Eval. 2019;12:10.
3. Şahin AE. Eğitim araştırmalarında Dephi tekniği ve kullanımı. Hacettepe Üniversitesi Eğitim Fakültesi Dergisi. 2001;20:215-220.
4. [No authors listed.] ACOG Practice Bulletin No. 207: Thrombocytopenia in Pregnancy. Obstet Gynecol. 2019;133:e181-e193.
5. Webert KE, Mittal R, Sigouin C, Heddle NM, Kelton JG. A retrospective 11-year analysis of obstetric patients with idiopathic thrombocytopenic purpura. Blood. 2003;102:4306-4311.
6. Neunert C, Terrell DR, Arnold DM, Buchanan G, Cines DB, Cooper N, Cuker A, Despotovic JM, George JN, Grace RF, Kühne T, Kuter DJ, Lim W, McCrae KR, Pruitt B, Shimanek H, Vesely SK. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv. 2019;3:3829-3866.
7. Provan D, Arnold DM, Bussel JB, Chong BH, Cooper N, Gernsheimer T, Ghanima W, Godeau B, González-López TJ, Grainger J, Hou M, Kruse C, McDonald V, Michel M, Newland AC, Pavord S, Rodeghiero F, Scully M, Tomiyama Y, Wong RS, Zaja F, Kuter DJ. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Adv. 2019;3:3780-3817.
8. Sun D, Shehata N, Ye XY, Gregorovich S, De France B, Arnold DM, Shah PS, Malinowski AK. Corticosteroids compared with intravenous immunoglobulin for the treatment of immune thrombocytopenia in pregnancy. Blood. 2016;128:1329-1335.
9. Bauer ME, Arendt K, Beilin Y, Gernsheimer T, Perez Botero J, James AH, Yaghmour E, Toledano RD, Turrentine M, Houle T, MacEachern M, Madden H, Rajasekhar A, Segal S, Wu C, Cooper JP, Landau R, Leffert L. The Society for Obstetric Anesthesia and Perinatology Interdisciplinary Consensus Statement on Neuraxial Procedures in Obstetric Patients With Thrombocytopenia. Anesth Analg. 2021;132:1531-1544.
10. Piel-Julian ML, Mahévas M, Germain J, Languille L, Comont T, Lapeyre-Mestre M, Payrastre B, Beyne-Rauzy O, Michel M, Godeau B, Adoue D, Moulis G; CARMEN investigators group. Risk factors for bleeding, including platelet count threshold, in newly diagnosed immune thrombocytopenia adults. J Thromb Haemost. 2018;16:1830-1842.
11. Patil AS, Dotters-Katz SK, Metjian AD, James AH, Swamy GK. Use of a thrombopoietin mimetic for chronic immune thrombocytopenic purpura in pregnancy. Obstet Gynecol. 2013;122:483-485.