RESEARCH ARTICLE
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Management of Primary Immune Thrombocytopenia – Turkish Modified Delphi-Based Consensus Statement for Special Considerations

Ümit E.G. et al: Management of Adult Primary ITP for Special Considerations

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Abstract

Introduction: Primary immune thrombocytopenia (ITP) is an acquired disorder of platelets with complex and unclear mechanism of increased immune distruction or impaired production of platelets. While management of ITP is evolving, there is a need for guidance particularly in certain circumstances such as pregnancy, emergency and for patients requiring co-

medications. We aimed to determine the tendencies of hematologists in Turkiye on such special conditions.
Methods: As a modified Delphi method, Turkish National ITP Working Group founded under Turkish Society of Hematology developed a questionnaire consisting of statements regarding pregnancy, emergency and circumstances regarding co-treatment with antiaggregant or anticoagulants. 107 Hematologists working either in university or state hospitals voted for their agreement or disagreement of the statements for two consequential rounds.
Results: Participant hematologists reached an agreement on the starting treatment in pregnant patients with platelets less than 30 $x10^9$/L and delivery of either normal or cesarian section to be safely performed above 50 $x10^9$/L. For emergency and rescue management of ITP, our panel have agreed against the use of high dose corticosteroids alone, preferred a combination with transfusion or IVIG. For patients who require interventions, platelet counts >50 $x10^9$/L were regarded as safe for low risk procedures as well as co-treatment with antiplatelets or anticoagulants.
Conclusion: As National ITP study group, we have observed the need to increase the practice guidance in patients with primary ITP requiring additional treatments including invasive interventions, and co-treatments towards coagulation. Decisions on the management of ITP during pregnancy should be individualized. There is a certain 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 the variations in the practices.
Key words: Adult primary immune thrombocytopenia, Management, Delphi method, Special considerations

Özet
Giriş: Primer immün trombositopeni, 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 Yöntem: 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 30 $x10^9$/L altına inmesi ile tedavi başlanması gerektiği ve 50 $x10^9$/L üzerindeki değerlerde normal ya da sezaryen doğumun güvenli olacağı konusunda görüş birliğine varmıştır. Acil ve kurtarma tedavilerine ilişkin olarak katılımcıların tek başına yüksek doz kortikosteroidden ziyade transfüzyon ya da IVIG ile kombine kullanımını tercih ettikleri gözlenmiştir. Düşük kanama riskli girişimsel işlemler ya da antiagregan veya antikoagulan gibi ek tedavi gereksiniminde 50 $x10^9$/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 Kelimler: 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 with increased peripheral destruction, lately recognized as a concept of immune dysfunction, impaired megakaryopoiesis or a complex interplay resulting with manifestations including bleeding and/or thrombosis (1). Treatment should be individualized and constructed around the patient's requirements including age, comorbidities and comedications and life style. Pregnancy, age related cardiovascular disorders may be challenging periods to manage in a patient with ITP and while the guidelines have been developed to adress these issues, treatments may vary within countries due to availability of the agents, economic disparities and distinctions of practices.

As the national ITP study group, we aimed to determine the perspectives of the practicing hematologists in Türkiye regarding the management of primary ITP (pITP) during pregnancy, emergency management for patients with bleeding or requiring surgical interventions and in conditions requiring antiaggregant or anticoagulant co-medication, and complement these perspectives of management with international data.

Methods

The Delphi method is a survey-based form of assessment of perspective. Statements were constructed and presented to the target population, evaluated and reckoned for a single or multiple courses until consensus or an adequate impression is obtained. The intended population vote anonymously and select their levels of agreement/disagreement. After the outcomes are collected, statements are appraised by the founder team to form a perspective of the target audience (2,3). Each individual statement was defined and framed on the statements within national international guidelines by the steering committee.

National ITP Study Group founded under Turkish Society of Hematology and Hemostasis and Thrombosis Scientific Subcommittee by Hematologists with expertise on ITP constructed a survey consisting 5 statements for pregnancy and 13 statements for emergency-rescue management or requiring co-medications. Each individual statement was defined and framed on the statements within national international guidelines by the steering committee. 107 hematologists of varying ages and facilities agreed to participate to the study. 88,3% of the votees were under 50 years and 40,2% was working in University Hospitals while the remaining 55,8% were working in State Hospitals.

The target audience were asked to consider each statement and select their level of agreement using a 5-point Likert-type scale (1=disagree-never, 2=somewhat disagree-rarely, 3=neither disagree-sometimes nor agree, 4=somewhat agree-often, 5=agree-always). Agreement of the statement was expressed as sum of percentage of votes that somewhat agree-often and agree-always.

Two rounds of voting were conducted with a halfway analysis to clear the statements when there was a lack of consensus and submitted for a second course. The second round of voting took place one month after the first, and the response rates for the rounds were 71,9% and 93,5% respectively. Results of the assessments were presented here, regardless of the level of agreement to be discussed.

Results

1. Pregnancy and ITP

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

Agreement: 98%
1.2 Statement: Treatment shall be commenced in pregnant patients presenting with <30 $x10^9$/L any time during pregnancy.
Agreement: 92%
1.3 Statement: For pregnant patients with ITP, platelet counts >70 $x10^9$/L is adequate for vaginal delivery.
Agreement: 92%
1.4 Statement: For pregnant patients with ITP, platelet counts >50 $x10^9$/L is adequate for cesarian section.
Agreement: 84%
1.5 Statement: For pregnant patients with ITP, platelet counts >70 $x10^9$/L is adequate for neuraxial anesthesia
Agreement: 80%
2. Emergency and Rescue Treatment of pITP
2.1 Statement: Pulse methyprednisolone should be administered in emergency situations requiring rapid platelet recovery.
Agreement: 28%
2.2 Statement: High dose dexamethasone (40mg/daily, 1-4days) should be administered in emergency situations requiring rapid platelet recovery.
Agreement: 39%
2.3 Statement: High dose dexamethasone (40mg/daily, 1-4days) combined with IVIG or platelet transfusion should be administered in emergency situations requiring rapid platelet recovery.
Agreement: 73%
2.4 Statement
Platelet transfusion can be administered for patients who have IVIG exposure in emergency situations requiring rapid platelet recovery.
Agreement: 40%
2.5 Statement
Antifibrinolytics shall be used in emergency situations as supportive treatment
Agreement: 40%
2.6 Statement: For patients who have pITP and not receiving treatment and will undergo an elective surgical intervention, corticosteroids and IVIG shall be used to increase platelet counts above safe thresholds.
Agreement: 67%
2.7 Statement: For patients who have pITP and not receiving treatment and will undergo an elective surgical intervention, TPO-RAs shall be used to increase platelet counts above safe thresholds.
Agreement: 8%
2.8 Statement: For patients with pITP, platelet counts 30-50 $x10^9$/L are safe for low risk surgical interventions under adequate local measures.
Agreement: 62%
2.9 Statement: For patients with pITP, platelet counts >50 $x10^9$/L are safe for low risk surgical interventions under adequate local measures.
Agreement: 94%
2.10 Statement: For patients with pITP, platelet counts >50 $x10^9$/L are safe for antiaggregant treatments.
Agreement: 90%
2.11 Statement: For patients with pITP, platelet counts >50 $x10^9$/L are safe for anticoagulant treatments.

Agreement: 86%

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

Agreement: 19%

2.13 Statement: For patients with pITP, platelet counts 30-50 x10^9/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 (<100 x10^9/L) is observed in less than 1 percent of uncomplicated pregnancies (4,5). Gestational thrombocytopenia (GT) is defined as a temporary condition isolated with mild thrombocytopenia observed in the late stages (majorly over 100x10^9/L) without any risk of bleeding or fetal complications and is the most frequent cause of thrombocytopenia during pregnancy (1,4). ITP is observed in 1-3/10.000 pregnancies and may be occur during any time of pregnancy. Severity of thrombocytopenia is variable and may decrease to levels less than 50 x10^9/L. Other causes of thrombocytopenia during pregnancy include preeclampsia with severe features, HELLP syndrome, disseminated intravascular coagulation, acute fatty liver of pregnancy and thrombotic microangiopathies (4-7). In our consensus assessment, our panel have agreed that for pregnant patients presenting with thrombocytopenia <70 x10^9/L, differential diagnosis including ITP should be investigated, as concordant with the international consensus report (7).

Management of ITP during pregnancy is mainly the same as in a non-pregnant patient and the goal of treatment is to reduce the risk of bleeding and to reach safe platelet counts for delivery rather than normalizing the platelet count. Treatment is not recommended by American Gynocology and Obstetrics Society, for patients who have platelet counts ≥ 30 x10^9/L and without bleeding until 36 weeks of gestation (or until delivery if it commences before) (4). While a stable platelet count may be aimed, to be on the safe side, our panel have agreed that treatment shall be commenced for pregnant patients with platelet counts < 30 x10^9/L. This observation may be interpreted as concordant with the consensus report and no thresholds have been recommended in 2011 American Society of Hematology guideline for starting treatment (6,7). For patients who have platelet counts <30 x10^9/L or with clinically relevant bleeding, oral corticosteroids or IVIG is recommended (1,4). Oral corticosteroids methyl prednisone and prednisolone are preferred to dexamethazone due to greater and more rapid placenta crossing of dexamethazone (8). Dose of corticosteroids is not clear, there is no evidence on the superiority of higher doses. Therefore, consensus recommendations have favored 0,25-0,5mg/kg daily doses.

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

Data regarding the use of TPO-RAs during pregnancy is limited and only based on case reports. Decision on the use of TPO-RAs during pregnancy shall be individualized and cannot be a routine practice for now. The goal of treatment for patients with ITP during pregnancy is ≥ 50 x10^9/L at the time of delivery. While data regarding safe platelet counts for neuraxial anesthesia is not available, 2021 consensus report from the Society for Obstetric Anesthesia stated that platelet counts >70 x10^9/L may be the safe recommendation to avoid epidural hematoma. Preferences of anesthesiologists may vary within countries and even within

centers and therefore the decision should be based on the multi-disciplinary team managing each patient.

Management of ITP during bleeding or in patients where rapid platelet recovery is required (surgical or medical interventions, etc), the treatment shall be individualized. Contributing factors for this decision include the severity of bleeding, age, comorbidities or comedications that may create an extra tendency for bleeding, complications of each ITP treatment and the time that is required or available for platelet increase. Though the bleeding risk is not exactly related with platelet counts, the risk may be regarded as increased when platelet counts are < 20 $x10^9$/L (11). For low risk procedures such as dental procedures including deep cleaning and simple extraction, ≥30 $x10^9$/L may be adequate while for complex extractions and minor surgeries, a level of ≥ 50 $x10^9$/L shall be targeted (7). Our panel have agreed that for low risk procedures, a platelet count ≥ 50 $x10^9$/L shall be regarded as adequate and the lack of agreement on platelet levels between 30-50 $x10^9$/L may be interpreted as the need to individualize ITP treatment as well as the risk of interventions being unclear.

Our panel have not reached a consensus on how to manage pITP patients in case of bleeding or when a rapid recovery is required. The major point that may be regarded as an agreement (73% of agreement) were observed on the combination of high dose dexamethasone with IVIG or platelet transfusions. While there is not enough data on the effectiveness of each option in emergency situations, combination of high dose corticosteroids with IVIG is stated as probably effective (7). Since TPO-RAs require at least 5 days to increase platelet counts, they are not recommended in emergency settings as our panel have not agreed on their use for rescue treatment as well as for rapid platelet recovery.

Platelet transfusions with or without IVIG may be considered in patients failing other treatments and an increase of platelet counts > 20 $x10^9$/L may be achieved in almost half of the patients though 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 though without any strong evidence. Our panel have not supported 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 the requirement of an antiplatelet or anticoagulant agent, our panel have agreed that platelet counts >50 $x10^9$/L is required. International consensus report have recommended a target level of ≥ 30-50 $x10^9$/L for single antiplatelet agent or anticoagulant treatment and ≥ 50-70 $x10^9$/L for dual antiplatelet or anticoagulants (7). Patients shall be assessed for their individual risk of bleeding including age, gender, bleeding history, fall risk, cancer and cancer treatments, co-medications and their social support and the target platelet count shall be based on this assessment.

Conclusion

Decisions on the management of ITP during pregnancy should be individualized and be conducted by a multidisciplinary team including hematology, obstetrics and anesthesiology. We have observed a certain 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 confidence may be due to the variations in the practices of the physicians who perform the interventions, as well as anxiety of hematologists which may be considered as patient or health care 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.U, M.Ayr., 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.U, M.Ayr., 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.U, M.Ayr., 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.U, M.Ayr., 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.U, M.Ayr., 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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Abbreviations: ITP: Immune thrombocytopenia

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