REVIEW ARTICLE

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Immune Thrombocytopenia

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A 25-year-old pregnant (3 months gestation) lady, who was a diagnosed case of Evans syndrome, on prednisolone 20 mg since past 4 months, presented with petechial rashes over the body for one week before presentation. She did not have fever, diarrhoea, vomitings, weight loss, bone pains, night sweats, Examination revealed anaemia, petechial rashes over limbs and abdomen, normal vitals, no lymphadenopathy, organomegaly, or sternal tenderness. Her baseline investigations revealed anaemia with thrombocytopenia of 15,000/cumm, peripheral smear showed thrombocytopenia with giant platelets, no abnormal cells. Hepatitis B, C and HIV serologies were negative. An anti-nuclear antibody test was negative, but a Direct Coombs test was positive. Urine examination and ultrasound abdomen were normal. A bone marrow exam was suggestive of normoblastic erythroid reaction, normal megakaryocytes and myeloid lineage. No abnormal cells or reticulin were seen.

A diagnosis of secondary ITP (Evans syndrome) was made. She was given methylprednisolone 1 gm iv/day over 3 days, but the platelet count did not improve. Subsequently, IVIG (2 gm/kg weight, divided over 5 days) was infused, and platelets increased upto 1,50,000/cumm but decreased again below 10,000/cumm.

Epidemiology, Pathogenesis and Management of ITP

ITP is an acquired immune destruction of platelets, defined as a platelet count less than 1,00,000/cumm[1]. It occurs in both adults and children, but while it is mostly a self-limiting disorder among children, in adults it is a chronic disorder.

Three seminal guidelines/consensus statements have been published in the field of ITP. In 2009, an International Working Group (IWG) of the European Haematology Association Scientific Working Group on Thrombocytopenias published recommendations for standardisation of definitions and terminology for research and clinical practice[2]. The American Society of Haematology (ASH) published a consensus report in 2010[3] and evidence based guidelines in 2011[4] for the diagnosis and management of ITP. Table I shows the important consensus definitions and criteria of ITP, from the IWG.

The incidence of primary ITP in adults is 3.3/100,000 per year with a prevalence of 9.5 per 100,000. There is a preponderance of females in younger patients (30 - 60 years), but among the elderly (> 65 years), the prevalence of ITP is almost equal among both genders[4-6]. Unfortunately, no data regarding incidence or prevalence has been published from India.

The pathophysiology of ITP is accelerated clearance of platelets coated by IgG anti-platelet autoantibodies. These antibodies recognise platelet surface glycoproteins such as glycoprotein IIb/IIIa, and Ib/IX or Ia/IIa[7] and are seen in 60 - 70% of patients. These antibody-coated platelets are then removed by macrophage phagocytosis, primarily in the spleen but also at other sites such as liver and bone marrow[8,9]. Other mechanisms incude direct activation of complement by antiplatelet antibodies[10] and diminished platelet production in the marrow, mediated by anti-megakaryocyte antibodies[11,12].

The incidence of refractory ITP was studied in six cohorts of patients initially diagnosed with ITP; less than 10% of cases could be labeled as refractory[13]. Refractory ITP exposes patients to continued risks of bleeding, toxicities from drugs, immunosuppresion, psychological and socio-economic consequences culminating in a poor quality of life. In a long-term follow-up study of 105 patients with ITP who were refractory to splenectomy, the majority of patients attained remission, either spontaneous or with treatment within 4 years. One-third required continuing treatment to maintain remission. Another 30% remained unresponsive and had significant morbidity and mortality. Sixteen per cent died of ITP; 10% from bleeding and 6% from therapy related complications[14]. In another study of 114 patients, 8% had refractory ITP and they had a 4-fold increased mortality compared with the general population, and a 4-fold increased morbidity compared with other ITP patients. Bleeding and opportunistic infections were equally

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responsible for deaths in the refractory patients[15]. The impact of chronic ITP on health related quality of life (HRQoL) was studied in 73 adult patients which tests domains like social functioning, vitality, mental health and emotional scores. Patients with ITP had remarkably poor HRQoL scores, significantly worse than the general population, than patients of hypertension and arthritis, and diabetes[16]. Treatments of ITP, especially steroids, are associated with significant morbidity and HRQoL scores were worse among patients taking these drugs for ITP than those not taking drugs[15].

The reasons why some patients are refractory are varied; continued destruction of platelets in liver and bone marrow, failure of compensatory megakaryopoiesis[11,17], and reduced thrombopoietin levels[18]. The approach to a patient of refractory ITP involves, first, to rule-out hidden causes (if not done so earlier). Testing for viral infections, autoimmune connective tissue diseases, bone marrow examination, flow cytometry of blood to look for lymphomas/leukaemias/PNH and cytogenetic analysis using FISH for MDS.

Once true refractory ITP is confirmed, the need for treatment must be ascertained. Close observation is sufficient for patients with platelet counts above 30,000/cumm, no or minor bleeding and an acceptable quality of life (HRQoL). At this point it is important to appreciate that poor quality of life (HRQoL) is an equally impotant indication for treatment, in patients who are not bleeding[16].

There is no consensus for one standardised treatment paradigm of refractory ITP. The goal is to maintain a safe platelet count (acceptable minor bleeding and minimal risk of major bleeding) using treatments chosen after considering availability, cost, patient preference, co-morbidities, and drug profiles, while minimising drug toxicity/side-effects. Available treatment modalities may be classified into those that are given only once to induce long-term remission (splenectomy, rituximab), and maintainence therapies to achieve sustained response (corticosteroids, immunosuppressive agents, thrombopoietin receptor agonists). Other, non-ITP, approaches directed at reducing bleeding without affecting platelet counts may also be used. For patients of refractory ITP failing first-line treatment (steroids, IVIG, Anti-D), there is no evidence-based, particular preference/ order for any of these modalities, save that they have been advocated as second-line and third-line therapies by the ASH[2]. The treating clinician must make individual decisions for patients regarding which drug(s) to be used, whether alone or in combination, after taking into consideration all factors. Table II lists the various treatment modalities for refractory ITP and their clinically relevant characteristics. The second-line therapies comprise a host of immunosuppressive agents with relatively lower response rates and/or greater toxicity. These drugs are often prescribed, not alone but, in combination with a first-line or another second-line drug with a different mechanism of action. Third-line drugs, which are of uncertain benefit and/or high toxicity with little supporting evidence, are reserved for the rare patient with serious bleeding who does not respond to first- and second-line therapies. Various algorithms and treatment strategies have been proposed for sequential and combined use of these drugs[9,19,33-40].

It must be appreciated that, as research advances, this list may undergo changes. Thrombopoietin receptor agonists (TRAs), which were grouped into third-line therapy by the ASH[2] have now been promoted to first-line therapy[19,20]. Similar is the case for rituximab, which was classified as second-line therapy by ASH; it is now considered as first-line therapy[19, 20]. In fact, the whole paradigm of refractory ITP may undergo a change as the watershed point of splenectomy is being questioned. This is because many patients (and their doctors) are now delaying/avoiding splenectomy for fear of post-operative complications, infections, increased risk of venous thrombosis, pulmonary hypertension and cardiac events or simply to allow time for spontaneous resolution[21,22]. Improvements in outcomes with rituximab and TRAs have led to these agents being used before splenectomy and recent data suggests that less than 25% of patients with ITP undergo splenectomy[23]. Hence, it is conceivable that, in the near future, the defiition of truly refractory ITP may include refractoriness to splenectomy, rituximab and/or TRAs and suggests a re-visit of the IWG definition of refractory ITP[24]. Even so, as of today, splenectomy remains the only treatment that provides sustained remission off all drugs at 1 year and beyond in a high proportion of patients with ITP (5 year response rates of 60 - 70%[25,26]); sustained remission rates with rituximab are disappointing (5-year response rates of 20%[27]), while the relapse rate after stopping TRAs is very high. A variety of combination regimens have also been used for treatment of refractory ITP, including cyclophosphamide, vincristine, prednisone, azathioprine, etoposide – overall response rate was 68%[28]. In a recent study, 37 patients of ITP refractory to splenectomy, rituximab, and TRAs were compared with 183 controls. Refractory ITP patients had a significantly higher rate of secondary ITP (35.1%), higher rates of bleeding at onset, low response rates to corticosteroids (68.6%), and a high mortality rate of 14%. An important finding in this study was that 7 of 10 patients with refractory ITP who were treated with a combination of TRAs and 1 of the immunosuppressive agents (mycophenolate mofetil, cyclosporine, cyclophosphamide, azathioprine, and haematopoietic stem cell transplantation) responded[29].

Table I: Definitions and criteria for ITP from the International Working Group (IWG).

Term Used	Definition	Remarks	
Primary ITP (80%)	Primary ITP is an autoimmune disorder characterised by isolated thrombocytopenia (peripheral blood platelet count less than 1,00,000/cumm) in the absence of other causes or disorders that may be associated with thrombocytopenia.	• The IWG defined the abbreviation in common use (ITP) to be immune thrombocytopenia (not idiopathic or purpura) because of a better understanding of the pathophysiology and also majority of patients do not present with purpura. The IWG also removed the term "acute" ITP, as this is a retrospective diagnosis and cannot be made in the beginning. • The diagnosis of ITP remains one of exclusion; no reliable clinical or laboratory parameters are currently available to establish it's diagnosis accurately. • Antiplatelet antibody testing is not indicated for the diagnosis of ITP, and both the ASH and the IWG guidelines do not recommend routine testing for antiplatelet antibodies	Other disorders associated with *non-immune thrombocytopenia* that must be excluded: • Liver disease • Alcohol abuse • Vitamin B12 deficiency • MDS • Environmental toxins • Myelophthisic disorders - metastases, Paget's disease, myelofibrosis • von Willebrand disease, type IIB • Inherited thrombocytopenias such as TAR syndrome, radioulnar synostosis, congenital amegakaryocytic thrombocytopenia, Wiskott-Aldrich syndrome, MYH9-related disease, Bernard-Soulier syndrome
Secondary ITP (20%)	All forms of *immune thrombocytopenia*, except primary ITP	• Atypical features/clues to a secondary cause include fever, significant lymphadenopathy, hepato-splenomegaly, anaemia disproportionate to the degree of bleeding, leukocytosis or leukopenia, abnormal cells on peripheral blood smear, deranged clotting screen, a systemically unwell patient and a family history of thrombocytopenia or bleeding. • The acronym ITP should be followed by the name of the associated disease for example, "secondary ITP (lupus-associated),"	Causes of Secondary ITP may be: • Antiphospholipid syndrome • Evans syndrome • Cytomegalovirus, *Helicobacter pylori*, hepatitis C, HIV, varicella zoster virus infections • CVID • Drugs - heparin, quinidine, valproate • Lymphoproliferative disorders • Bone marrow transplantation • Aplastic anemia, PNH, TTP • Systemic lupus erythematosus • Post-MMR vaccine
Newly Diagnosed ITP*	less than 3 months duration		
Persistent ITP*	3 - 12 months duration	Spontaneous remission not achieved or do not maintain a complete response following cessation of therapy	
Chronic ITP*	More than 12 months duration	Spontaneous remission not achieved or do not maintain a complete response following cessation of therapy	
Severe ITP*	Clinically relevant bleeding of sufficient magnitude to mandate treatment or requiring additional interventions or increase in drug dose		
Refractory ITP*	Presence of Severe ITP after splenectomy (includes both, primary failure and relapse after initial response - no time frame specified)	• Nonsplenectomised patients may be responders or nonresponders to various drugs, but should not be labelled refractory. • Refractory patients may respond temporarily to steroids or IVIG • These patients continually require therapies to increase and sustain a safe platelet count	The American Society of Haematology guidelines endorsed this definition of refractory ITP as a means of identifying the most severely affected patients.

** Applicable mainly for patients of Primary ITP (Table adapted and modified from Reference No. 1)*

ASH: American society of Hematology, CVID: Common variable immunodeficiency, HIV: Human Immune deficiency virus, IVIG: Intravenous immunoglobulin, IWG: International working group, MDS: Myelodysplastic syndrome, MMR: Measles, Mumps and Rubella, MYH9: May Hegglin anomaly, PNH: Paroxysmal nocturnal hemoglobinuria, TAR: Thrombocytopenia Absent Radii, TTP: Thrombotic thrombocytopenic purpura

Table II: Therapeutic options for patients of refractory ITP.

Drug and dose/regimen	Response rate	Response time	Sustained response rates	Toxicities	Average cost availability#
Dexamethasone 40 mg, oral daily for 4 days, every 2 - 4 weeks for 4-6 cycles@	upto 90%	1 - 4 weeks	50 - 80% at 2-3 years of follow-up	Mood swings, psychosis, weight gain, cushingoid facies, diabetes, osteoporosis, skin thinning, hypertension, dyspepsia, peptic ulcers, avascular necrosis, cataracts, opportunistic infections, adrenal insufficiency	Rs 350/- for 6 cycles @ 40 mg/day
Prednisolone, oral 0.5 - 2 mg/kg/day@	70 - 80%	1 - 4 weeks	Uncertain, less than 10% at low dose (< 5 mg/day)		Rs 5,000/- @ 60 mg day for 4 weeks
Methylprednisolone 500 - 1,000 mg per day for 3 - 5 days@	upto 95%	5 days	23% at 40 months		Rs 5,000/- @ 1,000 mg/ day for 5 days (hospitalisation costs extra)
Intravenous immunoglobulin, 0.4 gm/ kg/day for 5 days OR 1 gm/kg/day for 2 days@	Upto 80%, with 50% attaining normal platelet counts	24 - 48 hours	2 - 4 weeks	Headache, neutropenia, aseptic meningitis, renal failure, thrombosis, infusion reaction-flushing, fevre, chills, hypotension, diarrhoea Anaphylactic reaction in patients with IgA deficiency	Rs 1,85,000/- @ 120 gms, single cycle for a 60 kg patient (hospitalisation costs extra)
Anti-D immune globulin, intravenous, 50 - 75 mcg/kg@ @Indicated only in Rh(D) positive, nonsplenectomised patients	Upto 80%	5 days	3 - 4 weeks	Intravascular haemolysis, renal failure	Rs 24,000/- for single (hospitalisation costs extra) 3,000 mcg dose @ 50 mcg/ kg for a 60 kg patient
Azathioprine, 1-2 mg/kg, oral (maximum: 150 mg/d)	40 - 60%	3 - 6 months	Up to 25% patients maintain response, after stopping	Transaminits, severe neutropenia with infection, pancreatitis	Rs 6500/- per year - @ 100 mg/day
Cyclosporin-A, 5 mg/kg/d for 6 d then 2.5-3 mg/kg/d (aim for blood levels of 100 - 200 ng/ml)	30 - 60%, dose dependent	3 - 4 weeks	50% sustained remisssion at 2 years, while continuing low doses	Rise in serum creatinine, hyperkalaemia, hypertension, fatigue, paresthesias, gingival hyperplasia, hypertrichosis, tremor	Rs 50,000/- per year - @ 150 mg/dy
Cyclophosphamide (1 - 2 mg/kg oral, daily for at least 16 wk) or intravenous (0.5 - 1 g/m^2 every 2 - 4 weeks, upto 6 doses	24 - 85%	1 - 16 weeks	Up to 50% show a sustained response	Neutropenia, infections, transaminitis, haemorrhagic cystitis, nausea, vomiting	Oral - Rs 800/- for 4 months @ 100 mg/dayIV - Rs 2000/- @ 1000 mg dose for 6 doses (hospitalisation costs extra)
Danazol 200 mg 2 - 4 times oral, daily	10 - 70%	3 - 6 months	Upto 50% sustained remission, at a median of 6-13 years, after mean treatment of 3 years	Acne, amenorrhoea, increased facial hair, hypercholesterolaemia, transaminitis	Rs 43,000/- per year @ 800 mg/day
Dapsone 75 - 100 mg oral, once a day	40 - 75%	3 weeks	Sustained response in upto two-thirds of responders, after stopping	Methemoglobinaemia, haemolytic anaemia in patients with G6PD deficiency, severe skin rash	Rs 83/- year @ 100 mg/day
Mycophenolate mofetil 250 - 1,000 mg oral, twice daily	Up to 75%; complete response in up to 45%	4 - 6 weeks	Sustained for short time, after stopping	Dyspepsia, diarrhoea, anorexia, nausea, headache, bone marrow suppression, transaminitis	Rs 53,000/- per year @ 500 mg twice daily
Rituximab 375 mg/m^2 intravenous, weekly × 4 doses	60% of patients; complete response in 40% of patients	1 - 8 weeks	Sustained response at 5 years in 20-25% of responders. If re-treatment is required, response is good in those who had responded the first time	Infusion related fever/chills, rash, serum sickness and rarely bronchospasm, anaphylaxis, pulmonary embolism, retinal artery thrombosis, infection, and reactivation of hepatitis B. Rare cases of progressive multifocal leukoencephalopathy.	Rs 1,40,000/- per 2 gms @ 500 mg/dose × 4 doses

Eltrombopag 25-75 mg oral, daily	80% overall, 40 - 50% persistent	1 - 4 weeks	Up to 1.5 years, with continuous use	Headache in 20% of patients, increased bone marrow reticulin, rebound thrombocytopenia upon discontinuation, thrombosis, and liver function abnormalities	Rs 11,00,000/- per year @ 75 mg/day
Romiplostim 1-10 μg/kg subcutaneous, weekly	80% overall, 40 - 50% persistent	1 - 4 weeks	Up to 4 years, with continuous use	Headache, increased bone marrow reticulin, rebound thrombocytopenia upon discontinuation, thrombosis	Not available in India
Vinca alkaloid regimens: vincristine total dose of 6 mg (1 - 2 mg per infusion weekly); vinblastine total dose of 30 mg (10 mg per infusion weekly)	Variable and transient response in 10 - 75% of patients	1 - 2 weeks	75% of patients, monitored for upto 3 years, showed response	Peripheral neuropathy, neutropenia, fever, thrombophlebitis	Vincristine- Rs 300/- for 6 infusions vinblastine - Rs 1000/- for 3 infusions (hospitalisation costs extra)
Autologous Haematopoietic Peripheral Blood Stem Cell Transplantation[$31,32]	43%	5 weeks	Long-term complete remission in one-third of patients. Late relapses after 2 years seen	Neutropenia, infections, myelosuppression, Graft-versus-host disease, death	Rs 5,00,000 to 10,00,000/- (as per price list of Tata Memorial Hospital, Mumbai)
Combination chemotherapy using cyclophosphamide, vincristine, prednisone, azathioprine, aetoposide[$28]	68%, complete response in 40%	2 - 3 months	Durable response in two-thirds of patients achieving complete response	Neutropenia, infections, myelosuppression, late-onset malignancies, neuropahty, haemorrhagic cystitis	Drug costs, as above (hospitalisation and supportive blood component therapy costs extra)
Non-ITP therapies (which do not affect platelet count)	● Oral contraceptive pill or hormonal intra-uterine device, (e.g., Mirena®þ) to reduce menorrhagia ● Avoidance of non-steroidal anti-inflammatory drugs and other drugs that may interfere with platelet function - aspirin, clopidogrel ● Antifibrinolytic agents (especially for mouth and nose bleeding) - Tranaexemic acid, ε-aminocaproic acid ● Proton-pump inhibitors for gastritis				As per actual costs, when required SOS

Table from reference Nos. 1, 2, 3, 19 and 33.
#Checked from www.medguideindia.com and Compendium of Prices of National Pharmaceutical Pricing Authority (NPPA), Govt. of India - available on their website as http://www.nppaindia.nic.in/compendium2016.pdf. - accessed on 5th June, 2018.
@These (first-line) treatment options are typically used as add-on or rescue therapies, along with the other second or third line treatments.
$These (third-line) treatment options have minimal data and have potential for considerable toxicity.

Table III: Differential diagnosis of thrombocytopenia in pregnancy*.

Causes	Remarks
Gestational (incidental/benign) thrombocytopenia	Platelet counts > 70,000/cumm, appearing in late 2nd or 3rd trimesters, NO evidence of haemolysis, hypertension, proteinuria, coagulopathy, renal or CNS disease, platelet counts normalise soon after delivery
HELLP syndrome	Severely reduced platelet counts, appearing in 3rd trimester, transaminitis, haemolysis, coagulopathy
Preeclampsia	MIld thrombocytopenia, appearing in 3rd trimester, hypertension, proteinuria, renal and CNS involvement, seizures
Acute fatty liver of pregnancy	Mild thrombocytopenia, severe coagulopathy, appearing in 3rd trimester, hypoglycaemia, hyperuricaemia, transaminits, fulminant hepatic failure, renal disease

Characteristic features have been italicised and underlined
**Only causes, specific to the pregnant state, have been listed. Other causes are common with the non-pregnant state as in Table I*
CNS: Central Nervous System; HELLP: Haemolysis, Elevated Liver enzymes, Low Platelets

Table IV: Clinical aspects of ITP among pregnant women.

Clinical aspect	Remarks
Diagnosis	● Diagnosis of exclusion. ● A history of prior thrombocytopenia, autoimmune disease or severe thrombocytopenia (< 50,000/cumm) makes the diagnosis of ITP more likely. ● A significantly low platelet count in the first trimester, with a progressive decline as gestation progresses, is most consistent with ITP

	• All investigations, as in the non-pregnant state, to be performed.
Differential diagnosis	See table III
Important clinical variables to be gathered in assessment of a pregnany lady with ITP	• History of previous excessive bleeding in ante-partum/post-partum period or during labor • Neonatal platelet count and bleeding, in prior pregnancy • Exclude secondary causes of thrombocytopenia - HCV, HIV, SLE, APS, drugs, TTP • Rule-out other causes such as pre-eclampsia, HELLP - check BP, icterus, oedema, anaemia
Monitoring	• Monthly in the first and second trimester, every 2 weeks after 28 weeks, and weekly after 36 weeks. • Routine check, along with blood pressure, urine dipstick for protein, platelet count • Symptoms of bleeding - their severity and frequency
Ante-partum treatment	• Treatment goal is to maintain a safe platelet count in the mother, above 30,000/cumm • No treatment is recommended for asymptomatic mothers, with platelet count above 30,000/cumm in their first trimester • More aggressive treatment is recommended later in pregnancy (3rd or 2nd trimesters) to prepare the patient for labor and delivery, employing epidural anesthesia or caeseran section • Treatment has been recommended for women with a platelet count below 10,000/cumm at any time during pregnancy, or below 30,000/cumm in the second or third trimester, or when associated with bleeding[48,49]
Drugs/modalities which should be used	• Steroids - 1 mg/kg/day (pre-pregnancy weight) and titrated to lowest possible dose – may cause maternal hypertension, osteoporosis, hyperglycaemia, oro-facial defects in foetus • IVIG - 2 gm/kg, over 2 - 3 days, may be first choice agent also • Combination steroids + IVIG, for those refractory to either agent, alone • Laparoscopic splenectomy, in the 2nd trimester - for those refractory to steroids and/or IVIG
Drugs which should not be used	• Danazol • Cyclophosphamide • Vinca alkaloids
Drugs which MAY BE used with caution - FDA category C/D drugs (*for Refractory ITP)*	• Anti D immune globulin - 50 - 75 mcg/kg – for Rhesus positive women only • Azathioprine - 1 - 2 mg/kg/day – advised to check maternal TPMT levels before starting • Cyclosporine - 5 mg/kg/day, titrated to 2 - 3 mg/kg/day – monitor blood pressure, serum potassium and creatinine • Rituximab - 375 mg/m^2/week for 4 doses – check for hepatitis B, monitor for infections • TRAs - Eltrombopag, Romiplostim
Newer drugs which have been used in pregnancy	• Pegylated human recombinant megakaryocytic growth and development factor (PEG-rHuMGDF) • Recombinant thrombopoietin
Management during labour	• Mode of delivery is decided as per obstetric indication, and *not* as per platelet count of mother[3,48,49] • Foetal scalp or umbilical blood sampling is not recommended to check the baby's platelet count[2,3] • Minimum platelet count for vaginal delivery is 50,000/cumm; for epidural anesthesia or caeseran section, it is 80,000/cumm - may require IVIG and/or pulse IV steroids and/or platelet transfusions[2,3,49]
Neonatal considerations	• Transplacental transfer of anti-platelet IgG antibodies may cause fetal thrombocytopenia and neonatal bleeding during delivery - however, there is no correlation between the neonatal platelet count and the severity of maternal thrombocytopenia[50], or maternal antiplatelet IgG levels[51]. • The most reliable predictor of neonatal thrombocytopenia is a history of thrombocytopenia in the neonate at a prior delivery[52]. • Among 288 neonates born to women with ITP, platelet counts below 50,000/cumm were seen in 10.1%, while platelet counts below 20,000/cumm were found in 4.2% of the neonates[53]. • Intracranial haemorrhage is the most feared complication among neonates born to women with ITP. However, the risk of intracranial haemorrhage among neonates of women with ITP is very low, ranging from 0 - 1%[53,54] • Serial platelet counts should be monitored in all newborns at birth and during the first week of life; the onset of thrombocytopenia may be delayed. • ASH guidelines suggest that infants with a platelet count below 20,000/cumm, or those with haemorrhage, receive treatment with

	IVIG at a dose of 1 gm/kg[3] ● Imaging of the brain with ultrasonography, CT or MRI should be reserved for neonates with platelet counts of less than 50,000/cumm to look for intracerebral haemorrhage
Breast feeding	● No contraindication for breast feeding - no correlation found with neonatal thrombocytopenia[55] ● Women taking drugs, e.g., steroids, azathioprine, TRAs should be cautioned (cyclosporine is safe)
Future pregnancy	● Among 92 women with ITP, going through 119 pregnancies, those with previously diagnosed ITP were less likely to require therapy for ITP, than those diagnosed during pregnancy[56]. ● Women with the diagnosis of ITP prior to pregnancy had a higher incidence of foetal loss (11.2% vs 3.9%) and low birth weight for gestational age (17.9% vs 9.7%) than women diagnosed during pregnancy[57]. ● A higher incidence of premature birth is reported among women with pre-existing ITP[57,58]. ● DO NOT advise against pregnancy, unless previous one had severe consequences for mother and/or baby. Counsel regarding risks and emphasise upon high quality, multi-disciplinary ante-natal, intra-partum and neonatal care in such high-risk pregnancies.

APS: AntiPhospholipid Syndrome; BP: Blood Pressure; CT: Computed Tomography; HCV: Hepatitis C Virus; MRI: Magnetic Resonance Imaging; SLE: Systemic Lupus Erythematosus; TPMT: Thiopurine MethylTransferase.

The following are not justified for use in ITP due to evidence proving lack of efficacy and/or excessive toxicity: colchicine, interferon-alpha, protein A immunoadsorption column, plasmapheresis as an isolated approach, vitamin C, recombinant factor VIIa and Campath-1H[2].

On April 17, 2018, the US FDA granted marketing approval to a novel oral splenic tyrosine kinase inhibitor, Fostamatinib (Tavalisse®þ,Rigel Pharmaceuticals, Inc. San Francisco, USA) for use in adult patients with chronic ITP who have had an insufficient response to a previous treatment[30]. Fostamatinib is a tyrosine kinase inhibitor with demonstrated activity against spleen tyrosine kinase (SYK). The major metabolite of fostamatinib, R406, inhibits signal transduction of Fc-activating receptors and B-cell receptor. This reduces antibody-mediated destruction of platelets. A number of drugs have also been repurposed for use in refractory ITP, (e.g., decitabine, oseltamivir, sirolimus, and thalidomide), and are currently in clinical trials[19]. Several novel therapies are under investigation for the management of ITP. These include antibodies targeting the CD40-CD154 interaction between B and T cells[41,42], treatments targeting the Fc receptor, new Anti CD20 monoclonal antibody, veltuzumab[43], and novel agents to increase platelet production, including synthetic thrombopoietin[44], a new TRA (avatrombopag)[45], soluble TNF receptor (Etanercept)[46] and a radioprotector drug, amifostine[20].

Epidemiology and management of ITP in pregnancy

Thrombocytopenia complicates up to 10% of all pregnancies, and may result from a number of causes, the major chunk of which is due to gestational (incidental/ benign) thrombocytopenia. ITP affects 1 to 10 in 10,000 pregnancies[47]. ITP is the most common cause of isolated thrombocytopenia in the first and early second trimesters. The diagnosis of ITP may precede pregnancy, be diagnosed *de novo* during pregnancy, or be exacerbated during pregnancy. ITP, during pregnancy, entails multiple risks: obstetrical, haematological and neonatal, and that is why it is necessary to monitor the pregnant woman carefully. Further, it is not possible to predict neonatal prognosis in women with ITP and previous neonatal outcome may be used as a guide for neonatal risk of thrombocytopenia in successive pregnancies.

The presentation of ITP in pregnancy is much like that in the non-pregnant individual. Patients may be detected with asymptomatic thrombocytopenia on routine testing, or present with severe thrombocytopenia accompanied by bleeding manifestations. ITP should be suspected if severe, isolated thrombocytopenia is detected early in pregnancy. The differential diagnosis of thrombocytopenia during pregnancy includes conditions specific to pregnancy (Table III), besides causes common with the non-pregnant state. The major clinical considerations while managing a woman with ITP are listed in Table IV.

Rituximab (1 gram iv, repeated after 15 days) was used, unsuccesfully, and she again required IVIG. Due to continuing thrombocytopenia, with platelet counts dipping below 10,000/cumm, the patient underwent laparoscopic splenectomy in second trimester. After an initial response when platelets crossed 4,50,000/cumm, there was a drop to 1,00,000/cumm by 7th post-operative day reaching below 10,000/cumm by 12th post-operative day. She was confirmed refractory ITP, but, due to lack of further options, it was decided to monitor the patient on prednisolone 20 mg per day. Her platelet count continued to fluctuate between 10,000 and 30,000/cumm. At 36 weeks of gestation, she was admitted

with labour pains. Her platelet count which was 25,000/cumm, increased to 1,30,000/cumm after administering IVIG. She delivered a healthy baby by normal vaginal delivery, uneventfully. The baby's platelet count at birth was 2,40,000/cumm and was monitored for a week. At follow-up, she remained well on prednisolone 20 mg with platelet counts between 70,000 and 95,000/cumm. After 6 months, her steroid was tapered down to 5 mg per day. Within the next two months her platelet counts had decreased to 8,000/cumm while taking prednisolone 5 mg per day; the dose was increased to 20 mg and the counts increased to 24,000/cumm. She has not experienced any bleeding and remains under continuous follow-up; infant is doing well.

Conclusion

(a) The goal for treatment of ITP is to provide a safe platelet count (prevent major bleeding) rather than total correction of the platelet count – avoid unnecessary treatment of asymptomatic patients with milder degrees of thrombocytopenia.

(b) In a case of refractory ITP, regular clinical monitoring for bleeding, keeping the platelet counts above 30,000/cumm, an acceptable quality of life for the patient and no/minimal drug toxicity should be the objectives of management.

(c) Refractory ITP has varied therapeutic options, with variable response rates, toxicities, and costs – every clinician caring for such cases should be aware of these.

(d) Individualisation of therapy is a must, keeping in mind the drugs already used, their response (or failure) rates, co-morbid conditions, availability, cost, side-effects, and patient preference.

(e) Pregnancy is a complex situation demanding ever more thoughtfulness before selecting drugs – antepartum, labour and neonatal considerations should always be borne in mind.

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