CASE SERIES

Thrombocytopenia and the Impending Doom: A Case Series on Platelets Causing Obstetric Quandaries

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Abstract

Aim and background: Thrombocytopenia is defined as a decrease in the number of platelets. It is one of the, if not the most, common coagulation disorders that can complicate obstetrics. A normal count is arbitrarily set as 1,50,000–4,50,000 platelets per microliter.

Case description: Thrombocytopenia unique to pregnancy can be gestational thrombocytopenia, preeclampsia-induced thrombocytopenia, HELLP syndrome, and acute fatty liver of pregnancy (AFLP). While the remaining causes that coincide with pregnancy include disseminated intravascular coagulation (DIC), immune thrombocytopenic purpura (ITP), hematological malignancies, pseudothrombocytopenia, Wilson's disease, and autoimmune disorders. The former necessitate urgent delivery to optimize maternal and fetal outcome, following which there is spontaneous resolution of thrombocytopenia. While in the latter, pregnancy doesn't compound the issue and is a mere coincidence and hence the inciting factor needs to be eradicated to resolve the thrombocytopenia and often even requires use of blood products.

Conclusion: We attempt to discuss few cases of thrombocytopenia, seen at a tertiary care center and its multidisciplinary approach toward management.

Clinical significance: The unique problem with thrombocytopenia in obstetrics is the diagnostic hurdle it can pose to determine whether the pregnancy is a latter event to pre-existing thrombocytopenia, or if pregnancy is the causative factor for the same. This, in turn, can significantly alter the mode and time of termination and hence the neonatal outcome.

Keywords: Acute fatty liver of pregnancy, Acute myeloid leukemia, Dengue fever, Disseminated intravascular coagulation, Extrahepatic portal vein obstruction, HELLP syndrome, Immune thrombocytopenic purpura, Systemic lupus erythematosus, Thrombocytopenia, Wilson's disease.

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Introduction

Thrombocytopenia can have varied etiologies and here we attempt to discuss 10 different cases of thrombocytopenia in obstetrics and their course of management.[1] The cases included in this series are gestational thrombocytopenia that's classically a physiological phenomenon, immune thrombocytopenic purpura (ITP) which is an immune-based disorder, HELLP syndrome which pertains to form of severe preeclampsia that necessitates emergent delivery, pseudothrombocytopenia which is merely a vacutainer-related erroneous reporting and disseminated intravascular coagulation (DIC) due to various causes, including acute fatty liver of pregnancy (AFLP) which is a near fatal, complication due to depletion of coagulation factors and generalized thrombotic occurrences throughout the body. Also, we have discussed acute myeloid leukemia (AML) wherein there is cancerous suppression of platelet production and dengue fever wherein there's viral suppression of the same, extrahepatic portal venous obstruction (EHPVO) and Wilson's disease which causes splenic sequestration and destruction of platelets.

Grossly speaking, there is either a reduced production or excessive destruction and utilization of platelets that leads to thrombocytopenia. We elucidate each of these aforementioned disorders below.

Case Description

Case 1 : Gestational Thrombocytopenia

A 32-year-old G2P1L1, with history of cesarean section in previous pregnancy, registered at our center at 8 weeks of gestation, was seen to have decreasing trend in the platelet count from 26th week of gestation till term. The nadir was attained when the patient presented in labor at 38 weeks of gestation with platelet count of 60,000 platelets per microliter. Her hematological workup was carried out in her antenatal period, which was negative for autoimmune disorders, preeclampsia or HELLP syndrome or any bone marrow-related aplasia. A diagnosis of exclusion, gestational thrombocytopenia, was given and since the patient was not willing for a trial of labor, emergency lower segment cesarean section was carried out after transfusion of random donor platelets. A female baby weighing 2.9 kg was delivered and a hemogram was carried out for the baby to check for neonatal thrombocytopenia,

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which was within normal range. The mother had an uneventful postoperative course and her platelets had recovered to normal range spontaneously after 6 weeks of gestation.

Case 2: Immune Thrombocytopenic Purpura

A 22-year-old primigravida, booked at our tertiary care hospital at 12 weeks of gestation was diagnosed with thrombocytopenia (55,000 per microliter) on her first visit on routine hemogram study. She gave no history of any event of bleeding through gums, petechiae, joint pain, or heavy menstrual bleeding. A similar workup to earlier mentioned patient was carried out and direct Coombs test was found to be positive. A provisional diagnosis of ITP was given. Her peripheral blood smear showed presence of severe thrombocytopenia with giant platelets. Bone marrow aspirate smear showed presence of normocellular bone marrow with increased megakaryocytes. All these features were suggestive of peripheral immune destruction of platelets, thereby confirming the diagnosis of ITP.[2] Hematology team's assistance was sought for management of this patient, who advised pulsed steroid therapy with methyl prednisolone 500 milligram for 3 days followed by oral prednisolone on tapering doses to lowest tolerated dose. Intravenous immunoglobin was advised as well in a dose of 1 gm/kg body weight. These measures increased the platelets from a low of 25,000 cells per microliter in 3rd trimester to 60,000 cells per microliter. The patient was transfused with random donor platelets at term, when the patient presented in labor, prior to the cesarean section that was eventually carried out for fetal distress due to passage of meconium. The post operative course was uneventful and patient continued prednisolone and discharged. The neonate was tested for thrombocytopenia and was not diagnosed in it.

Case 3: HELLP Syndrome

A 23-year-old primigravida, was referred to our emergency obstetric services department at 37 weeks of gestation in view of deranged serum parameters. She had hyperbilirubinemia (total bilirubin: 4 mg/dL) with a predominantly direct component (3.39 mg/dL), altered liver transaminases (200–300 IU/liter), altered lactate dehydrogenase (600 U/liter) and thrombocytopenia (80,000 cells per microliter). A diagnosis of HELLP syndrome, stage II according to Mississippi classification was made. Her blood pressure was measured to be 210/100 mm of Hg and urine albumin showed +3 on dipstick test. Other vital parameters were within normal range. Intravenous labetalol was given slowly to lower the blood pressure. A fundoscopic examination was done to check for papilledema, which was normal. The patient was induced for labor in view of her preeclampsia and HELLP syndrome with prostaglandin E2 analog gel. The patient had fetal distress with passage of meconium in active stage of labor for which emergency cesarean section was undertaken. Post delivery, there was gradual improvement in her blood parameters. She was started on oral labetalol and nifedipine in tapering doses titrated to control her hypertension. A high protein diet was supplemented to recover for the hypoproteinemia.

Case 4: Pseudothrombocytopenia

On multiple occasions, routine hemogram shows presence of thrombocytopenia which on peripheral smear shows giant platelets due to clumping of multiple platelets together. The cause of this clumping is the ethylenediaminetetraacetic acid (EDTA) agent present in vacutainers that aids in the same. Doing a manual platelet count after using heparinized vacutainers, helps solve this problem and hence avoid unnecessary interventions.

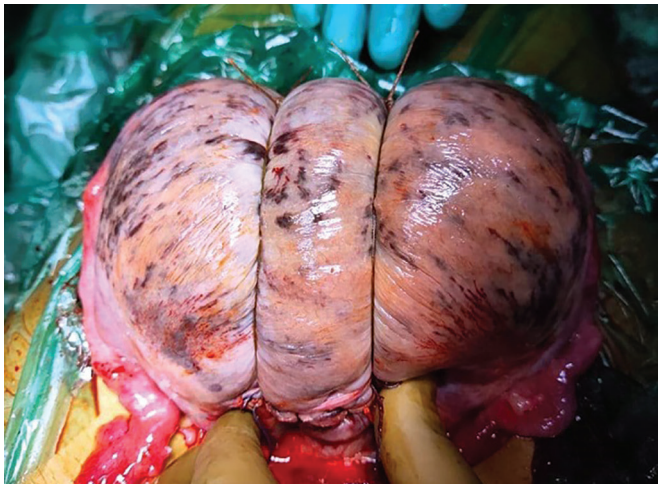

Fig. 1: Hayman's uterine compression sutures

Case 5: Disseminated Intravascular Coagulation

A 23-year-old primigravida, presented to the emergency services department with pain in abdomen at 33 weeks of gestation. She gave history of absent fetal movements for 6 hours and passage of clots per vaginum. On examination, she had severe pallor, pulse of 120/minute, blood pressure of 100/60 mm of Hg. On abdominal examination, a full term, tonically contracted uterus was felt and fetal heart sounds could not be localized on handheld Doppler. Per vaginal examination revealed presence of intact membranes and active labor. Artificial rupture of membranes was done and it revealed presence of blood-stained liquor, suggestive of abruptio placentae. Blood investigations showed the presence of severe anemia (hemoglobin – 6 gm/dL), thrombocytopenia (45,000 cells per microliter), reduced hematocrit (18%). Coagulopathy with INR of 1.9 and serum fibrinogen of 114 mg/dL and raised d-dimer levels were seen. Ultrasound studies confirmed intrauterine fetal demise and showed a retroplacental clot. The patient had a central line inserted for fluid monitoring by invasive method. A total of 2 packed red cells, 6 fresh frozen plasma, 2 cryoprecipitate pools were transfused. The patient delivered spontaneously and vaginally a male baby of 1.7 kg. Blood clots measuring 350 grams were evacuated after the delivery of placenta. The patient had a bout of atonic postpartum hemorrhage refractory to uterotonics and balloon tamponade so exploratory laparotomy was done and Couvelaire uterus was seen. Hayman's uterine compression sutures were taken as shown in Figure 1 with chromic catgut no. 2 as compression test was positive. Patient was looked after in the intensive care unit and had hypertension later that was managed with oral hypertensives. Breast milk suppression therapy was given.

Case 6: Acute Myeloid Leukemia

A 25-year-old primigravida, referred to our outpatient department in view of peripheral tingling sensation, low-grade intermittent fever episodes, oral ulcers, and gradually increasing hypertrophy of gums since a month. She was 34 weeks by gestation and her hemogram showed anemia (hemoglobin 8.4 gm/dL), leukocytosis (34,550 cells per microliter) and thrombocytopenia (1,00,000 cells per microliter). Peripheral smear showed blast cells predominantly (more than 80%) with majority being myeloblasts as seen in Figure 2. Mature leukocytes were almost absent, erythrocytes were severely hypochromic and normocytic to macrocytic and

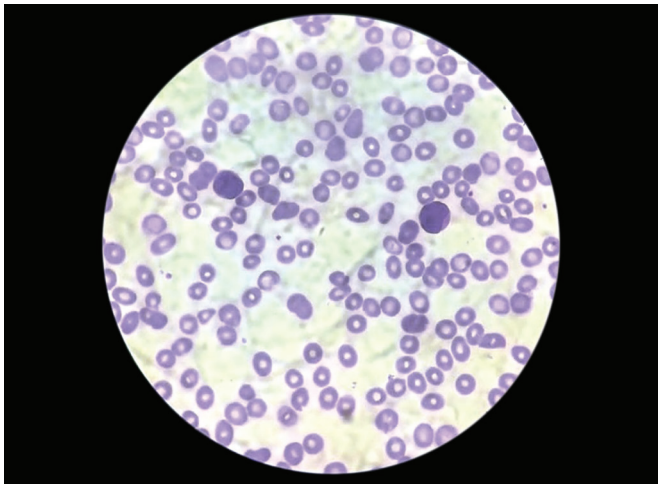

Fig. 2: Peripheral blood smear with myeloid like blast cells in AML

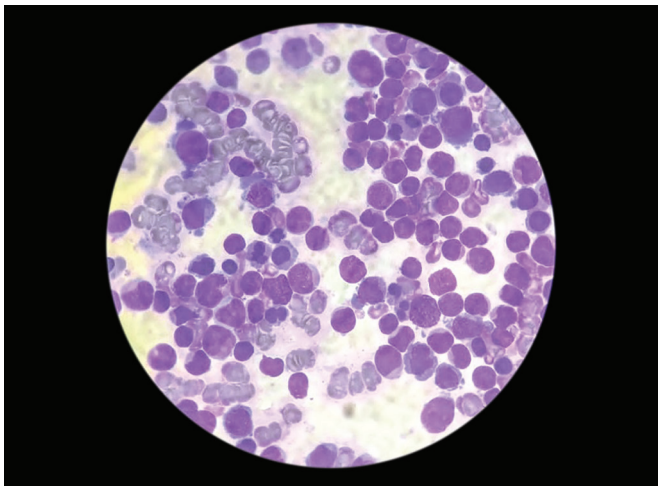

Fig. 3: Bone marrow aspirate showing more than 80% myeloid blast cells

giant platelets seen. A bone marrow study was performed as per hematologist's advice and diagnosis of AML was confirmed as seen in Figure 3.[3] Corticosteroids were given to the mother for fetal lung maturation and cytarabine and doxorubicin chemotherapy to suppress excessive blast cells was initiated. Cesarean section was done using vertical midline abdominal incision and a male baby of 2.5 kg delivered. The patient was post operatively admitted to oncology care unit where she was continued on chemotherapy and started on broad-spectrum antibiotics. Breast milk suppression was carried out to avoid chemotoxic effects on the baby through lactation. She had repeated spikes of fever with rapidly depleting counts of leukocytes, giving rise to febrile neutropenia. Owing to the likelihood of sporadic form of the cancer, the neonate was not subjected to genetic tests for the same. At the time of publication of this article, the patient awaited risk stratification test reports and potential bone marrow transplant.

Case 7: Dengue Fever

A 32-year-old primigravida, was admitted from emergency medical services for high-grade fever with chills for 2 days at 35 weeks of gestation. The fever was undulating, with petechial rashes seen all over the body, relieved on antipyretic agents. A preliminary hemogram showed thrombocytopenia (platelet count 60,000 cells per microliter). The patient was diagnosed of dengue fever due to positive NS1 antigen test. Serial monitoring of the platelets was done and a nadir of 18,000 cells per microliter was reached 6 days after the onset of fever. Since there were signs of hemorrhage, platelets were not transfused and the patient was kept on symptomatic management in the intensive care unit with daily non stress test to confirm fetal well-being. The patient was discharged after an increasing trend was seen in the platelet counts and currently, she is on routine antenatal follow up at the time of publication.

Case 8: Extrahepatic Portal Venous Obstruction

A 22-year-old G2P1L1 with a prior normal delivery, known case of EHPVO since the age of 5 years, with portal hypertension was registered at our tertiary care institute, at 28 weeks of gestation. Her liver biopsy done earlier was normal, while bone marrow aspirate showed hypercellular. Her esophagogastroduodenoscopy showed presence of esophageal varices, with no history of recent episode of hematemesis. The routine hemogram showed thrombocytopenia (platelet count of 53,000 cells per microliter) likely due to hypersplenism, and anemia (hemoglobin 6.5 gm/deciliter) possibly due to anemia of chronic disease and hypersplenism. The serum lactate dehydrogenase levels were marginally raised while her autoimmune workup was within normal limits. Fetal growth monitoring was normal on ultrasound and the patient was transfused a pint of packed red cells for severe anemia and later discharged for routine antenatal outpatient monitoring.

Case 9: Acute Fatty Liver of Pregnancy

A 35-year-old G5P3L3A1 with previous normal deliveries, referred to emergency medical services department at 35 weeks of gestation in view of altered sensorium for 1 day. The patient's pulse and blood pressure could not be recorded and fetal cardiac activity could not be seen on ultrasound. The patient was shifted to intensive care unit and initiated on inotropic support and mechanical ventilation. The patient's husband gave history of patient having nausea, decreasing appetite, and generalized weakness for 3 days. Examination revealed icterus. Blood investigations revealed acute kidney injury with raised serum creatinine (3.4 mg/dL), raised serum ammonia (70 µg/dL), leukocytosis (23,000/mcL), thrombocytopenia (45,000/mcL), coagulopathy (INR 2.3), and hyperbilirubinemia (total bilirubin 5.6 mg/dL) with raised transaminases. Her hepatic viral markers were negative. In accordance with Swansea criteria, a provisional diagnosis of AFLP was made. The patient succumbed 2 days later. Autopsy report of the liver confirmed the provisional diagnosis.

Case 10: Wilson's Disease

A 21-year-old primigravida, known case of Wilson's disease since 8 years, with chronic liver disease, portal hypertension, and splenomegaly, registered antenatally at 17 weeks of gestation at our center.[4] She consumed d-penicillamine and zinc sulfate for copper chelation. She had raised urine copper levels (134 mg/24 hours) and reduced serum ceruloplasmin levels (2.59 mg/dL). She had thrombocytopenia due to hypersplenism, with the lowest count recorded at 50,000 cells per microliter. Her magnetic resonance imaging study of the brain showed hyperintense lesions in the basal ganglia which explained her dysarthria and ataxia. Slit-lamp examination showed the characteristic Kayser–Fleischer ring in her

eyes as shown in Figure 4. The patient had a spontaneous vaginal delivery at 37 weeks of gestation that required transfusion of platelets perinatally and then had an uneventful postnatal course.

Discussion

Thrombocytopenia in pregnancy, as currently defined by international working group, stands at a platelet count of 1,00,000 cells per microliter.[1] While most of the thrombocytopenia etiologies resolve post-delivery, few persist irrespective of the obstetric status.

The primary set of investigations should involve evaluating all the routine ones that monitor other systemic involvement. In patients with hepatic and renal dysfunction accompanying thrombocytopenia, a generalized endothelial dysfunction has to be anticipated and the likelihood of a morbid pregnancy-related disorder like HELLP syndrome, DIC, or AFLP is increased. The only measure required is to accentuate fetal delivery in these patients, who might require intensive care monitoring. In patients with hepatic and renal are unaffected, a lookout for an inciting hematological disorder by evaluating peripheral blood smears, bone marrow biopsy, and autoimmune affliction should be done. Doing an abdominal ultrasound in these patients carries immense diagnostic value to look for splenic sequestration and thereby extravascular hemolysis. The differentiation between these disorders is necessary as the termination of pregnancy for a non-pregnancy-related thrombocytopenia can lead to morbidities to the fetus due to its premature delivery, without improving the maternal outcome significantly. Also, without deriving the causative factor for these disorders, mere transfusion of blood products to correct thrombocytopenia will only predispose the female to transfusion-related complications without actually correcting the cause of that thrombocytopenia, throwing the treating obstetrician and the patient in an endless, vicious loop of treatment.

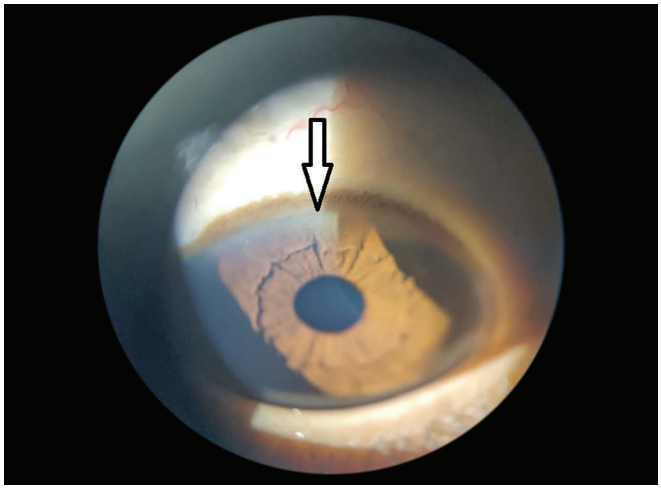

Fig. 4: Kayser–Fleischer ring on ocular slit-lamp examination in Wilson's disease

Gestational thrombocytopenia as discussed earlier, was thought of as a result of hemodilution earlier, is now being understood to have more etiology than one. Antibody formation against platelets, sequestration into placenta, changes in activity of von Willebrand factor, increased macrophage activity are few of the recently proposed mechanisms which also explain its recurrence in subsequent pregnancies and the non-uniformity of its causation in all pregnant women. Immune thrombocytopenic purpura can be an antibody mediated as well as T-cell-mediated disease. It has an increased occurrence alongside other autoimmune disorders. Disseminated intravascular coagulation is a classic example of dysregulation and imbalance between procoagulant and anticoagulant pathways which leads to depletion of platelets, either due to blood loss or increased consumption across all vessels. Acute myeloid leukemia is a disease of myeloid precursor cells where there's increased blast cell proliferation in the bone marrow, leading to overcrowding and eventual decreased production of other precursors. This leads to increased risks of infections, bruising, and fatigue. While most cases are sporadic, genetic tests are indicated for the neonate to determine the risk of inheriting the disease.

Dengue fever is caused the bite of female Aedes mosquito, as the virus spreads through its saliva, and then leads to bone marrow suppression and resulting pancytopenia, especially thrombocytopenia. This can lead to postpartum hemorrhage whereas antenatally increased chances of preterm birth and low birth weight babies and poorer neonatal APGAR scores are seen through various studies.[5] Extrahepatic portal venous obstruction leads to thrombocytopenia due to splenic sequestration due to splenomegaly caused by portal hypertension arising from blockage in the portal system outside the liver. Acute fatty liver of pregnancy is caused by defective fatty acid metabolism in the mitochondria of fetus, caused by long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency. This results in increased fatty acids in the mother leading to deleterious effects on liver and its sequelae as stated through Swansea criteria.[6] Wilson's disease is an autosomal recessive disorder that is caused by ATP7B enzyme deficiency leading to impaired copper metabolism and deposition in the body leading to toxicity (Table 1) encapsulates the same.

Table 1: A summary capsule on thrombocytopenia in pregnancy

Sr. No.	*Name*	*Investigations*	*Management*
1.	Gestational thrombocytopenia	a. Complete hemogram b. Antinuclear antibodies c. Liver function tests d. Serum lactate dehydrogenase e. Peripheral smear	a. Expectant management b. Spontaneous resolution postnatally c. Advise on risk of recurrence in subsequent pregnancy
2.	Immune thrombocytopenic purpura	a. Complete hemogram b. Antinuclear antibodies c. Peripheral smear d. Bone marrow aspirate studies	a. Pulsed steroid therapy with methyl prednisolone b. Oral prednisone therapy c. Platelets transfusion d. Neonatal testing for thrombocytopenia

(Contd...)

Table 1: *(Contd...)*

Sr. No.	*Name*	*Investigations*	*Management*
3.	HELLP syndrome	a. Complete hemogram b. Liver function tests c. Serum lactate dehydrogenase d. Peripheral smear e. Fetal Doppler ultrasound	a. Maternal blood pressure monitoring b. Magnesium sulfate therapy c. Termination of pregnancy d. Spontaneous resolution postnatally
4.	Disseminated intravascular coagulation	a. Complete hemogram b. Coagulation studies c. D-dimer assay d. Bleeding and clotting time e. Liver and renal function tests. f. Obstetric ultrasound	a. Correction of coagulopathy b. Termination of pregnancy c. Uterotonics d. Uterine compression sutures e. Invasive fluid monitoring f. Correction of anemia due to blood loss
5.	Acute myeloid leukemia	a. Complete hemogram bone marrow aspirate studies b. Peripheral smear c. Genetic studies	a. Cytotoxic chemotherapy b. Breast milk suppression c. Broad-spectrum antibiotics d. Bone marrow transplantation
6.	Dengue fever	a. Complete hemogram b. NS1 antigen test and dengue virus IgM status c. Serial platelets monitoring	a. Symptomatic management with antipyretic agents and parenteral fluids
7.	Extrahepatic portal venous obstruction	a. Complete hemogram b. Peripheral smear c. Liver function tests d. Abdominal ultrasound and porto-systemic Doppler studies e. Esophago-gastro-duodenoscopy f. Coagulation studies	a. Platelets transfusion b. Variceal banding or ligation c. Anemia correction
8.	Acute fatty liver of pregnancy	a. Complete hemogram b. Liver and renal function tests c. Coagulation studies d. Serum ammonia e. Hepatic viral markers f. Blood glucose levels	a. Blood and blood components b. Termination of pregnancy c. Inotropic support d. Mechanical ventilation e. Invasive fluid monitoring
9.	Wilson's disease	a. Complete hemogram b. Liver function tests c. Abdominal ultrasound and porto-systemic Doppler studies d. Esophago-gastro-duodenoscopy e. Urine copper f. Serum ceruloplasmin g. MRI of brain h. Slit-lamp examination i. Partner's genetic testing	a. Copper chelation with d-penicillamine and zinc sulfate b. Platelets' transfusion
10.	Systemic lupus erythematosus	a. Complete hemogram b. Antinuclear antibody c. Anti-ds DNA antibody d. SS-A and SS-B antibodies e. Renal function tests f. Urine routine and microscopy g. APL antibodies h. Obstetric ultrasound	a. Immune suppressant agents b. Corticosteroids c. Low-dose aspirin

Conclusion

The above cases brief us about the maternal and neonatal outcomes and diverse range of diagnostic algorithms to achieve an optimal outcome.

Clinical Significance

The diagnosis of the etiology of thrombocytopenia becomes crucial as barring a few, most of them can continue beyond pregnancy and the ones that accompany pregnancy can determine the fetal outcome by altering the timing of termination of pregnancy. Following a systemic approach toward diagnostic tests with an astute clinical acumen can help in securing a timely diagnosis and to map the further plan of management.

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