Thrombocytopenia in Pregnancy

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Abstract: Thrombocytopenia is the second commonest hematological abnormality during pregnancy. In majority of cases platelet counts revert back to normal after pregnancy is over. However, in some cases, the disease is more serious and if not managed properly leads to increased maternal mortality and morbidity and may also manifest fatal haemorrhages in neonates. Detailed history and physical examination with properly directed laboratory tests usually facilitate in early diagnosis and reduced morbidity and mortality.

Key words: Thrombocytopenia, gestational thrombocytopenia, ITP, HELLP syndrome, pregnancy induced hypertension

Thrombocytopenia is the second most common hematologic abnormality during pregnancy, anemia being the most common.1,4 Thrombocytopenia occurs in approximately 10% of pregnant women.5 Thrombocytopenia is defined as a platelet count below 150 x10⁹/l, caused by accelerated platelet destruction or decreased production. It is clinically graded as:

- Mild with a platelet count of 100-150 x 10⁹/l
- Moderate at 50–100 x 10⁹/l
- Severe with less than 50 x 10⁹/l

Thrombocytopenia in pregnant women may result from a variety of causes ranging from mild disorders such as gestational thrombocytopenia to life threatening conditions such as HELLP syndrome (hemolysis, elevated liver function tests, and low platelet syndrome), and low platelet syndrome. The clinical features of many of these disorders often overlap making their diagnosis difficult and it is for these complicated cases for which hematologic consultation is taken; Therefore, a thorough knowledge and familiarity of clinical and laboratory features of each of these disorders and differentiation of benign from malignant disorders is essential for an accurate diagnosis and appropriate management.

Some causes are related to pregnancy particularly whereas some of the cases are due to some underlying cause that was undiagnosed previously and has become clinically overt only during pregnancy.6

The overall frequency of thrombocytopenia during pregnancy is about 8%, but when patients with obstetric or medical conditions are excluded, the frequency drops to 5.1%.1 In this review, we discuss the differential diagnosis of the more common causes of pregnancy-associated thrombocytopenia, their diagnosis and give an overview of approaches to hematologic management.7

The most common cause for thrombocytopenia during pregnancy is gestational thrombocytopenia, accounting for almost 3/4th of all cases. Hypertensive diseases (eclampsia, pre-eclampsia, HELLP syndrome) account for 21% of cases. Immune thrombocytopenias (ITP and neonatal alloimmune thrombocytopenia) account for 4.1% cases.8

All these conditions must be included first in differential diagnosis of low platelet counts in pregnant females as they result in considerable morbidity and mortality and thus must be sorted meticulously and thus managed accordingly. Other less common causes include SLE, Rheumatic diseases, DIC, TTP, APL syndrome, drugs, fatty liver and rarely infection with HIV.

Gestational Thrombocytopenia

Gestational thrombocytopenia (GT) is the diagnosis of exclusion and has following characteristic features:

- Thrombocytopenia is mild to moderate with platelet count not less than 70 x 10⁹/l.
- Preconception or early pregnancy platelet count is normal
- There is no history of thrombocytopenia before pregnancy
- There is no history of bleeding from any site
- Platelet count returns to normal within 2-12 weeks after delivery

GT should be differentiated from idiopathic thrombocytopenia in which platelet count is usually lower before pregnancy. In most of these cases there is a previous history of bleeding. The mechanism of GT is not clear. Increased platelet consumption and increased plasma volume are probably the two contributory factors.
Gestational thrombocytopenia does not have any adverse effect on mother or fetus or neonate, and no management is necessary except for regular monitoring.

**Pregnancy induced hypertension (PIH) and HELLP syndrome**

PIH and HELLP syndrome are the major causes of maternal and perinatal mortality and morbidity worldwide, particularly in developing countries. Preeclampsia affects approximately 6% of all pregnancies, most the primigravidas less than 20 or greater than 30 years of age and accounts for 17.6% of maternal deaths in the United States. Thrombocytopenia in PIH is usually moderate; rarely the platelet count falls below 20 x 10^9/l. Hemorrhage is uncommon unless associated with DIC. A slowly decreasing platelet count may be observed before the clinical manifestations are overt. Though the pathogenesis of thrombocytopenia in patients with preeclampsia is not well understood, it may involve enhanced platelet clearance due to adhesion of circulating platelets to damaged or activated endothelium, accelerated platelet activation due to hemostatic system activity and thrombin generation, and/or clearance of IgG-coated platelets by the reticuloendothelial system. The HELLP syndrome is often considered to be a variant of preeclampsia and is associated with significantly greater maternal and fetal morbidity and mortality than preeclampsia. Criteria for the diagnosis of HELLP syndrome include:

1. Microangiopathic hemolytic anemia (MAHA)
2. Elevated liver enzymes
3. Thrombocytopenia, with a platelet count below 100 x10^9/l

HELLP syndrome is associated with both maternal and neonatal complications. Patients with HELLP syndrome are at increased risk of disseminated intravascular coagulation, renal failure, consumptive coagulopathy, abruptio placenta, pulmonary and cerebral edema, subcapsular liver hematoma, and hypovolemic shock. Fetal complications of HELLP syndrome include perinatal death, IUGR and preterm delivery.

The offsprings of mothers with HELLP and preeclampsia may also become thrombocytopenic; though thrombocytopenia may not develop until after delivery. Although elevated levels of platelet-associated IgG may be present on the platelets of these neonates, these do not correlate with the development or severity of thrombocytopenia. More recent studies have suggested a contribution of impaired megakaryocytogenesis. The causes of thrombocytopenia from pregnancy-induced hypertension and HELLP syndrome are unknown. Abnormal vascular tone with resultant accelerated platelet destruction, platelet activation, and coagulation defects are different mechanisms that are thought to be implicated. The increased levels of platelet-associated immunoglobulin G (IgG) that has been detected in patients with pregnancy-induced hypertension are nonspecific and do not necessarily form an immunologic basis for the thrombocytopenia. Activation of the coagulation cascade occurs in most patients with preeclampsia. Though routine studies such as the PT, aPTT, and fibrinogen level usually remain normal, levels of more sensitive markers of hemostatic activity such as fibrinogen, D-dimers and thrombin–antithrombin complexes are elevated to a variable extent in most patients who develop thrombocytopenia. Activation of hemostasis is unlikely to be the primary cause of thrombocytopenia in these patients, however, it is associated with more severe intrauterine growth retardation.

### Table 1: Causes of Thrombocytopenia During Pregnancy

<table>
<thead>
<tr>
<th>Cause</th>
<th>Description</th>
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<tbody>
<tr>
<td>Gestational Thrombocytopenia</td>
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<tr>
<td>Immune thrombocytopenic Purpura</td>
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<tr>
<td>Pre-eclampsia and HELLP Syndrome</td>
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<tr>
<td>Thrombotic thrombocytopenic purpura (TTP)</td>
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<tr>
<td>Hemolytic uremic syndrome (HUS),</td>
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<tr>
<td>Disseminated intravascular coagulation (DIC),</td>
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<tr>
<td>Systemic Lupus Erythematosus (SLE)</td>
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</tr>
<tr>
<td>Anti-phospholipid antibodies syndrome (APLA)</td>
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<tr>
<td>Drugs</td>
<td></td>
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<tr>
<td>Folate deficiency</td>
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<tr>
<td>Aplastic anemia</td>
<td></td>
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<tr>
<td>Infections e.g. Malaria, HIV, etc</td>
<td></td>
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<tr>
<td>Hypersplenism</td>
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</table>

HELLP syndrome appears to be initiated by microvascular damage that results in platelet activation. Degranulation of the platelets is followed by vasospasm and further endothelial damage. HELLP syndrome is associated with an increased risk of disseminated intravascular coagulation and is associated with both maternal and neonatal complications. Patients whose pregnancies are complicated by HELLP syndrome are at a higher risk for renal failure, consumptive coagulopathy, abruptio placenta, pulmonary and cerebral edema, subcapsular liver hematoma, and hypovolemic shock. Fetal complications of HELLP syndrome include perinatal death, IUGR, preterm delivery and neonatal thrombocytopenia.

**Management:** Management of preeclampsia and/or HELLP is supportive, and should be focused on medically stabilizing the patient and managing them conservatively till 34 weeks. Patients with disseminated intravascular coagulation are at risk of catastrophic bleeding complications secondary to rapid consumption of platelets and coagulation factors. Platelet transfusions may be
administered to raise the platelet count prior to cesarean section, though the survival of transfused platelets in patients with preeclampsia is diminished. If required, the coagulopathy resulting from preeclampsia-associated DIC should be managed with fresh frozen plasma or cryoprecipitate in case of severe DIC resulting in hypofibrinogenemia.

Preterm neonates of mothers with pregnancy induced hypertension are at risk for neonatal thrombocytopenia and resulting bleeding complications, such as excessive bleeding from blood draws or circumcision, mucosal bleeds in the gastrointestinal tract, cephalohematomas, subgial bleeding, and intracranial hemorrhages. Full-term infants have no specific risk when considering bleeding complications but are at an increased risk for intrauterine growth retardation. In most cases, the clinical manifestations of preeclampsia resolve within several days after delivery; however, the platelet count may remain diminished for an additional 24–48 hours. Occasional patients experience prolonged thrombocytopenia accompanied by an elevated LDH and multi organ dysfunction after delivery. These manifestations may be reversed to some extent by plasma exchange and/or corticosteroids.

It is very important to differentiate HELLP syndrome from other causes of thrombocytopenia like ITP, TTP, HUS, DIC and AFLP (Acute fatty liver of pregnancy) so that treatment may be instituted accordingly. ITP is differentiated by presence of antibodies and absence of other features seen in HELLP syndrome. Microangiopathic hemolytic anemias are differentiated by peripheral blood findings and other laboratory findings. AFLP typically occurs between the 30th and 38th gestational weeks with a 1 to 2 week history of malaise, anorexia, nausea, vomiting, mid epigastric or right upper abdominal pain, headache and jaundice. Hypertension and proteinuria are usually absent. Table 2 depicts a brief list of drugs which are known to cause thrombocytopenia by variable mechanisms, and a good clinical history must always take into account the recently administered drugs.

### Immune thrombocytopenia purpura (ITP)

As in non-pregnant patients, the pathogenesis of ITP during pregnancy involves the actions of antiplatelet antibodies that recognize specific platelet glycoproteins. These antibody coated platelets are then cleared by the reticuloendothelial system, primarily the spleen. It is the most common cause of significant thrombocytopenia in the first trimester. A history of prior thrombocytopenia, underlying autoimmune disease or severe thrombocytopenia (platelet count <50 x10^9/l) are suggestive of ITP. Moreover it is usually associated with neonatal thrombocytopenia. Five characteristics of immune thrombocytopenic purpura make the diagnosis likely:

1. moderate thrombocytopenia (50–100 x 10^9/l),
2. a preconception or early gestation platelet count that is less than 100 x 10^9/l,
3. normal to increased megakaryocyte number as determined by bone marrow biopsy,
4. exclusion of other systemic disorder or use of drugs that might be associated with decreasing platelet counts, and
5. an absence of splenomegaly.

### Risk of Thrombocytopenia to mothers with ITP and their off springs

Pregnancy does not seem to worsen the course of immune thrombocytopenic purpura, but cases of severe thrombocytopenia can cause serious morbidity and mortality to the mother and fetus. The mother is at risk for spontaneous hemorrhage, particularly if the platelet count drops to less than 20 x10^9/l. The maternal IgG will cross the placenta and may cause fetal thrombocytopenia. This condition is manifested by purpura, ecchymosis, melena, and even intracranial hemorrhage in the neonatal period. Between 10-20% of these neonates are delivered with platelet counts below 50 x10^9/l, while platelet counts may be less than 20 x10^9/l in 5%. Bleeding complications at the time of delivery develop in 25–50% of severely thrombocytopenic neonates. However, intracranial hemorrhage is rare. Currently, there is no proven maternal treatment to decrease the incidence of fetal

### Table 2. Drugs causing Thrombocytopenia

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
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<tbody>
<tr>
<td>Antibiotics</td>
<td>Ampicillin, Penicillin, Rifampin</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Thiazides, Furosemide</td>
</tr>
<tr>
<td>Analgesics</td>
<td>Aspirin, Acetaminophen, Indocin</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Phenytoin, Valproic Acid, Carbamazepine</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Methylldopa, Heparin, Digitalis, Ranitidine, Cimetidine, Procainamide, Gold compounds, Cis-platinum, Cyclosporin</td>
</tr>
</tbody>
</table>

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thrombocytopenia. Of all parameters the most reliable predictor of fetal thrombocytopenia is a history of thrombocytopenia at delivery in a prior sibling. 26

Moreover, since the neonatal platelet count may decline for 4-5 days after delivery, daily monitoring is indicated, and therapy for immune thrombocytopenia should be instituted if it develops over this interval.

Management of Pregnant women with ITP

The goal of treatment of patients of ITP is remission and not cure. 27 Therapy of pregnancy-associated ITP should focus on the management of thrombocytopenia in the mother and decision about mode of delivery. Decisions concerning the need for therapy are determined by the absolute platelet count and whether active bleeding is present. Patients with platelet counts greater than 30 x 10^9/l and no bleeding generally do not require treatment. However, in the presence of more severe thrombocytopenia, or bleeding, therapy should be initiated. 28 Moreover, as pregnancy approaches term, more aggressive measures to raise the platelet count to a level sufficient to ensure adequate hemostasis during delivery, should be instituted. Most studies suggest that a platelet count >50 x 10^9/l is sufficient in this regard, though some recommend a platelet count > 100 x 10^9/l as a cut-off level. 29 Corticosteroids are considered to be first line of therapy because of their efficacy and low cost. 30 However due to their toxicities such as hypertension and diabetes, continuous monitoring of blood pressure and sugar is mandatory. Moreover it may also promote premature rupture of the fetal membranes. Therefore, some experts have suggested that high dose (2 gm/kg) intravenous immunoglobulin (IVIg) should be employed as first-line therapy for pregnancy-associated ITP. However, since responses to IVIg are often transient, multiple courses of therapy during gestation may be required and also due to economical constraints and patient inconvenience their use as first line therapy for ITP in pregnant patients remains controversial. IVIg should at least be strongly considered when more than 10 mg/day of prednisone is required to maintain the maternal platelet count above 30 x 10^9/l. IVIg may also be useful in raising the platelet count in preparation for delivery. In patients who do not respond satisfactorily to corticosteroids or IVIg, an option of splenectomy is seriously considered.

Splenectomy, if required, should be performed in the second trimester, as surgery early in pregnancy may induce premature labor, and splenectomy in the third trimester may be technically difficult due to obstruction of the surgical field by the gravid uterus. 31 A small subset of thrombocytopenic patients do not respond satisfactorily to corticosteroids, IVIg or splenectomy, and other approaches must be considered. Intravenous anti-D has also been used with success in a small number of pregnant women, though its safety has not been established. A role immunosuppressive and cytotoxic agent is still controversial, and these are better avoided particularly in early pregnancy. 32,33

Mode of Delivery of an ITP Mother

Majority of obstetricians now manage pregnant females with ITP very well and do not opt for cesarean section as was previously done. Mortality from complications of general anesthesia was shown to be 16.7 times that of regional anesthesia. 34 Spinal and epidural anesthetics are the anesthetic techniques of choice in obstetric practice whereas general anesthesia is generally reserved for emergency situations. The absolute number of platelets considered safe for the performance of a spinal block (to avoid hematoma formation) is still debatable. Regional anesthesia has been administered safely to patients with mild thrombocytopenia (platelet count 70 x 10^9/l). 35 Cesarean section is performed only if there is evidence of fetal platelet count < 50 x 10^9/l or for some obstetric complications. Platelet transfusion may be required at the time of delivery if mother is severely thrombocytopenic or is clinically bleeding. 36

Neonatal Alloimmune Thrombocytopenia (NAIT)

NAIT is the platelet equivalent of red cell hemolytic disease of newborn. It affects 1 in 1,000-2,000 live births and causes considerable morbidity and mortality in neonates. It results from maternal alloimmunization to fetal platelet antigens, which are recognized as foreign by maternal immune system particularly PLAI inherited from father. The maternal immune system produces IgG antiplatelet antibodies which cross the placental barrier and cause platelet destruction. One difference between Rh disease and neonatal alloimmune thrombocytopenia is the occurrence in the first pregnancy. Fifty percent of neonatal alloimmune thrombocytopenia cases are discovered in the first live-born infant, 31 and subsequent pregnancies are affected in similar to increasing severity. Most cases are diagnosed after delivery. The maternal history and pregnancy are unremarkable, and the platelet count is often normal. Neonates manifest evidence of severe thrombocytopenia either at delivery or during the first few hours of life. Petechiae or ecchymoses appear over the fetal presenting part, their platelet count is severely depressed, and they have considerable bleeding when circumcised or when blood is drawn. The most serious complication, intracranial hemorrhage, occurs in 10% to 20% of all infants affected and occurs in utero 25% to 50% of the time. 37

Microangiopathies Leading to Thrombocytopenia

Thrombotic thrombocytopenic purpura (TTP), Hemolytic uremic syndrome (HUS) and DIC share the central features of MAHA and thrombocytopenia. Though neither disease occurs exclusively during pregnancy, they may get exacerbated during pregnancy. 38 Thrombotic thrombocytopenic purpura (TTP) is a rare but life-threatening disease characterized by microangiopathic
hemolytic anemia and consumptive thrombocytopenia leading to disseminated microvascular thrombosis. This results in a variety of signs and symptoms from organ ischemia which includes pentad of symptoms that include MAHA, thrombocytopenia, neurologic abnormalities, fever, and renal dysfunction. The clinical manifestations of HUS are similar, though while neurologic abnormalities are usually more prominent in patients with TTP, renal dysfunction is more severe in patients with HUS. Levels of ADAMTS13 are markedly decreased in most patients with TTP. ADAMTS13 deficiency can be either congenital or acquired. Congenital deficiency is caused by reduced synthesis of ADAMTS13 due to genetic defect. Acquired TTP is, at least in part, caused by inactivation and removal of ADAMTS13 from plasma due to the development of anti-ADAMTS13 auto antibodies. It has been found that levels of ADAMTS13 decrease during normal pregnancy, and is one of the factors causing predisposition to development of thrombotic microangiopathy in this condition. TTP and HUS may be difficult to differentiate from one another, as well as from other pregnancy-specific causes of thrombocytopenia such as preeclampsia or the HELLP syndrome. The extent of microangiopathic hemolysis is generally more severe in TTP or HUS than in preeclampsia or HELLP, and the former disorders are not associated with hypertension. Another feature that distinguishes these disorders is their response to delivery. While preeclampsia or the HELLP syndrome usually improve following delivery, the course of pregnancy-associated thrombotic microangiopathies does not; hence pregnancy termination should not be considered therapeutic in patients with TTP or HUS. Thus differentiation of TTP from other MAHA is very important as platelets are contraindicated in this condition rather it is managed with fresh frozen plasma. TTP responds equally well to plasma exchange in pregnant and non-pregnant patients. Plasma therapy may be less effective for pregnancy associated HUS, at least with regard to reversal of renal dysfunction. Nevertheless, encouraging results have been observed by some groups, and thus a therapeutic trial of this plasma exchange is indicated. Patients with TTP are thus managed with FFP till their platelet count is > 70,000 till surgery is planned. Pregnancy-associated HUS is associated with long-term maternal morbidity, including chronic renal insufficiency and hypertension. The placental ischemia and increased incidence of premature delivery that complicate pregnancies in patients with thrombotic microangiopathies often lead to poor fetal outcomes. Fetal monitoring is an important part of management. Disseminated intravascular coagulation may complicate several obstetrical disorders, including preeclampsia, placental abruption, amniotic fluid embolism, uterine rupture, and retention of a dead fetus, and may result in thrombocytopenia. Differentiation of both these conditions from DIC is also very important which has some underlying cause, is associated with decrease in coagulation factors and fibrinogen, accentuation of fibrinolytic system along with thrombocytopenia and thus management depends upon correction of underlying cause first and replacement of coagulation factors, fibrinogen, platelets and heparin therapy if required.

**Acute fatty liver of pregnancy (AFLP)**

AFLP affects one of every 5000–10,000 pregnancies, and is most common in primaparas during the third trimester. It is reported to be more common in twin rather than singleton pregnancy. Women with AFLP present with malaise, nausea, epigastric and right upper quadrant pain, dyspnea, mental status changes, and cholestatic liver abnormalities. Diabetes insipidus may also occur, and hypoglycemia is common and often severe. Levels of fibrinogen and antithrombin are severely depressed, and 75% of patients manifest a prolonged PT accompanied by laboratory evidence of disseminated intravascular coagulation, perhaps related to decreased hepatic synthesis of antithrombin. The extent of microangiopathic hemolysis and thrombocytopenia is generally mild compared to that observed in HELLP, TTP, or HUS. Management of patients with AFLP is supportive, focusing on correction of hypoglycemia and electrolyte imbalances, as well as the underlying coagulopathy. Up to 10 days after delivery may be required for normalization of hemostatic abnormalities. Fetal mortality in this disorder approaches 15%, though maternal mortality occurs in less than 5% of cases.

**Other causes of pregnancy-associated thrombocytopenia**

As in the non-pregnant setting, HIV infection should be considered in any thrombocytopenic patient with risk factors. Likewise 25% of patients with systemic lupus erythematosus (SLE) develop thrombocytopenia secondary to platelet destruction due to antiplatelet antibodies, circulating immune complexes or other causes. Antiphospholipid antibodies (APLA) may also be associated with preeclampsia in addition to thrombosis and recurrent fetal loss. The possibility of congenital platelet disorders etc should always be kept in mind as many of these may be diagnosed by careful examination of the peripheral blood film. Pseudothrombocytopenia, an in vitro artifact attributable to platelet clumping caused by EDTA-dependent antiplatelet antibodies, may be transferred from mother to fetus following transplacental passage of the offending antibody. Finally drug-induced thrombocytopenia occurs in the pregnant as well as the non-pregnant women. History of drug intake ad it’s with drawl is the first step in management of these patients.

**Workup for Maternal Thrombocytopenia**

While determining the cause of thrombocytopenia during pregnancy a detailed medical history, physical examination, gestational age at which thrombocytopenia is recognized,
Obstetrical history, platelet count and other laboratory tests help to narrow down the differential diagnosis. For example thrombocytopenia in early pregnancy and history of preconception thrombocytopenia is more in favor of ITP. Whereas gestational thrombocytopenia is not seen in early pregnancy, preconception platelet count is normal and counts return to normal in postpartum period. For late gestational age or 3rd trimester thrombocytopenia differential diagnosis includes PIH, HELLP syndrome, TTP, HUS, DIC and AFL. All these conditions must be ruled out by relevant laboratory tests.

Degree of thrombocytopenia also provides some clue, as it is mild to moderate in gestational thrombocytopenia, and is more severe in other cases. Similarly there is usually no bleeding in GT but there is usually history of bleeding in ITP and more so with microangiopathies.

Thrombocytopenia occurring during pregnancy should be properly investigated, as with consultation of both obstetrician and hematologists these cases can be diagnosed early and thus managed properly.

References


