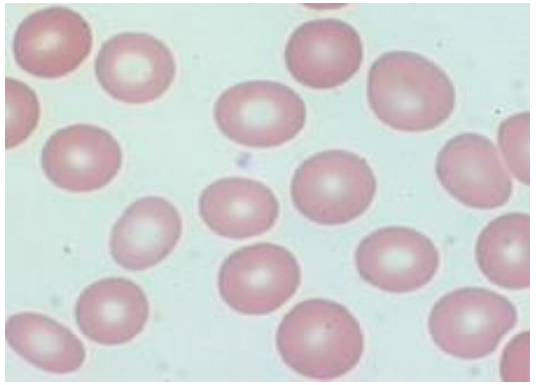

Thrombocytopenia in pregnancy

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NHS Foundation Trust

Guideline for the management of Thrombocytopenia in pregnancy (GL927)

CHANGES IN PLT COUNTS cont/

- Thrombocytopenia in pregnancy is the 2nd most common haematological finding after anaemia
- Can be physiological or pathological
- Affects 7-10% of all pregnant women
- Thrombocytopenia is a drop in platelet count < 150 x10^9/L
- Platelets 120-150 x10^9/l are frequent in the 3rd trimester

1.0 Overview:

Thrombocytopenia occurs in 8-10% of all pregnancies. The severity is classified as follows

- Mild: >100
- Moderate: 50 -100
- Severe: <50

In pregnancy most cases are mild and benign, but it can be associated with severe complications for mother and baby.

In cases where the platelet count is <80, discussion with a consultant haematologist is advised.

2.0 Signs (usually only present if platelets <50):

- Petechiae
- Nose bleeds
- Rarely: haematuria, gastrointestinal bleeding.

3.0 Possible Causes:

Diagnosis	Proportion	Pathophysiology
Gestational Thrombocytopenia	About 75%	Physiological dilution, accelerated destruction
Immune Thrombocytopenic Purpura (ITP)	About 3%	Immune destruction, suppressed production
Thrombotic Thrombocytopenic Purpura (TTP)		Peripheral consumption, microthrombi
Haemolytic Uraemic Syndrome (HUS)		Peripheral consumption, microthrombi
Pre-eclampsia, Eclampsia, Haemolysis, Elevated liver enzymes and low platelet count syndrome (PET, HELLP)	About 15-20%	Peripheral consumption, microthrombi

Hereditary thrombocytopenia		Bone marrow underproduction
Pseudo thrombocytopenia		Laboratory artefact
Viral infections: HIV, Epstein-Barr virus		Secondary autoimmune thrombocytopenia
Medications: heparin-induced		Bone-marrow suppression
Leukaemia/Lymphoma		Failure of Platelet production, bone marrow infiltration
Severe Vitamin B12 or Folate Deficiency		Failure of Platelet production
Splenomegaly		Splenic Sequestration

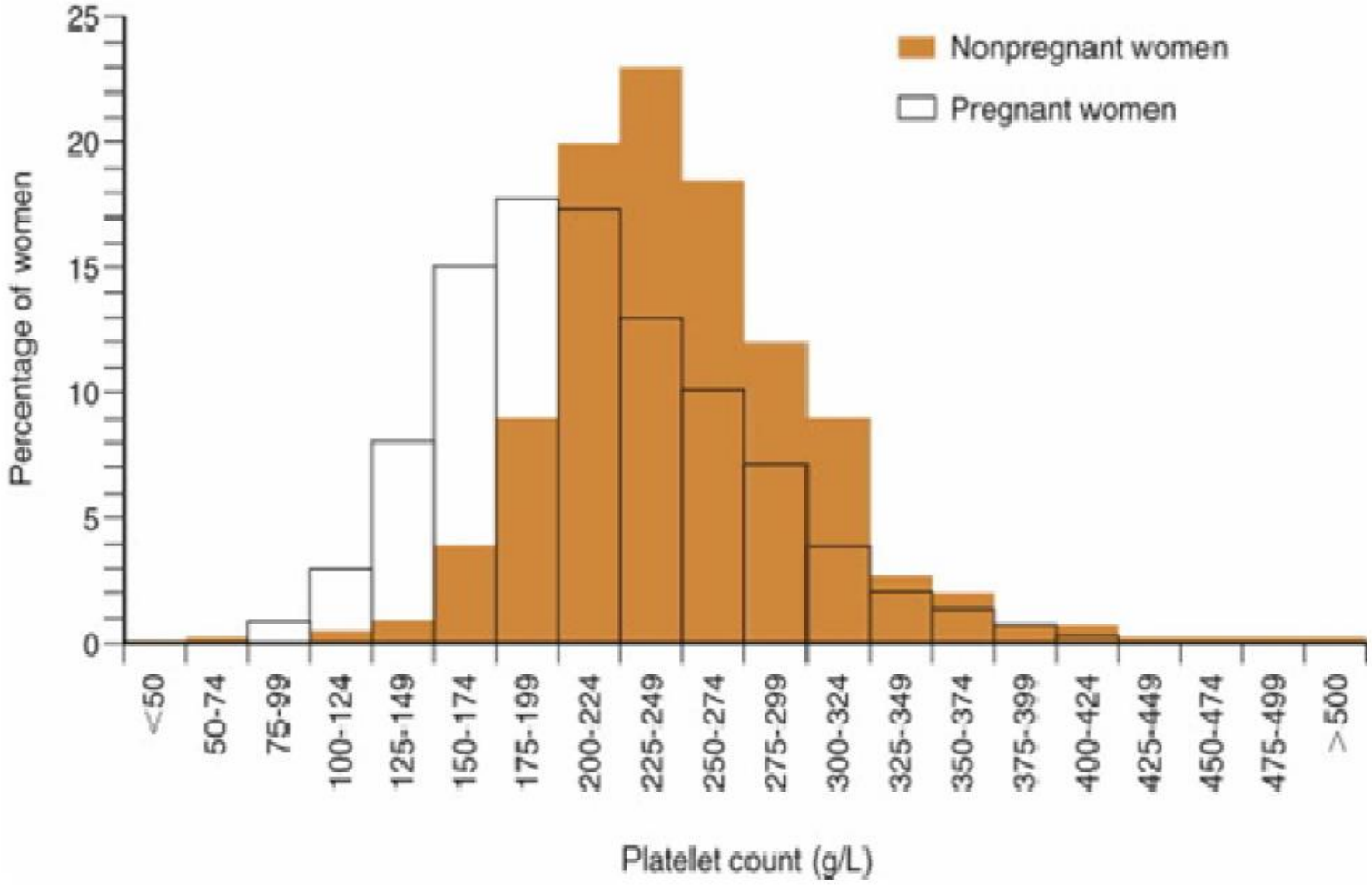


Figure 11. Histogram of platelet counts of pregnant women in the 3rd trimester compared to non pregnant women

Reference- Proceedings in Obstetrics and Gynecology 2013. Maternal thrombocytopenia in pregnancy.

Bleeding complications

- Pregnant women with thrombocytopenia have fewer bleeding complications compared to non pregnant women due to

  pro-coagulant state induced by increased levels of: 1. Fibrinogen

  2. Factor VIII
  3. von Willebrand factor
  4. Suppressed fibrinolysis
  5. Reduced protein S activity

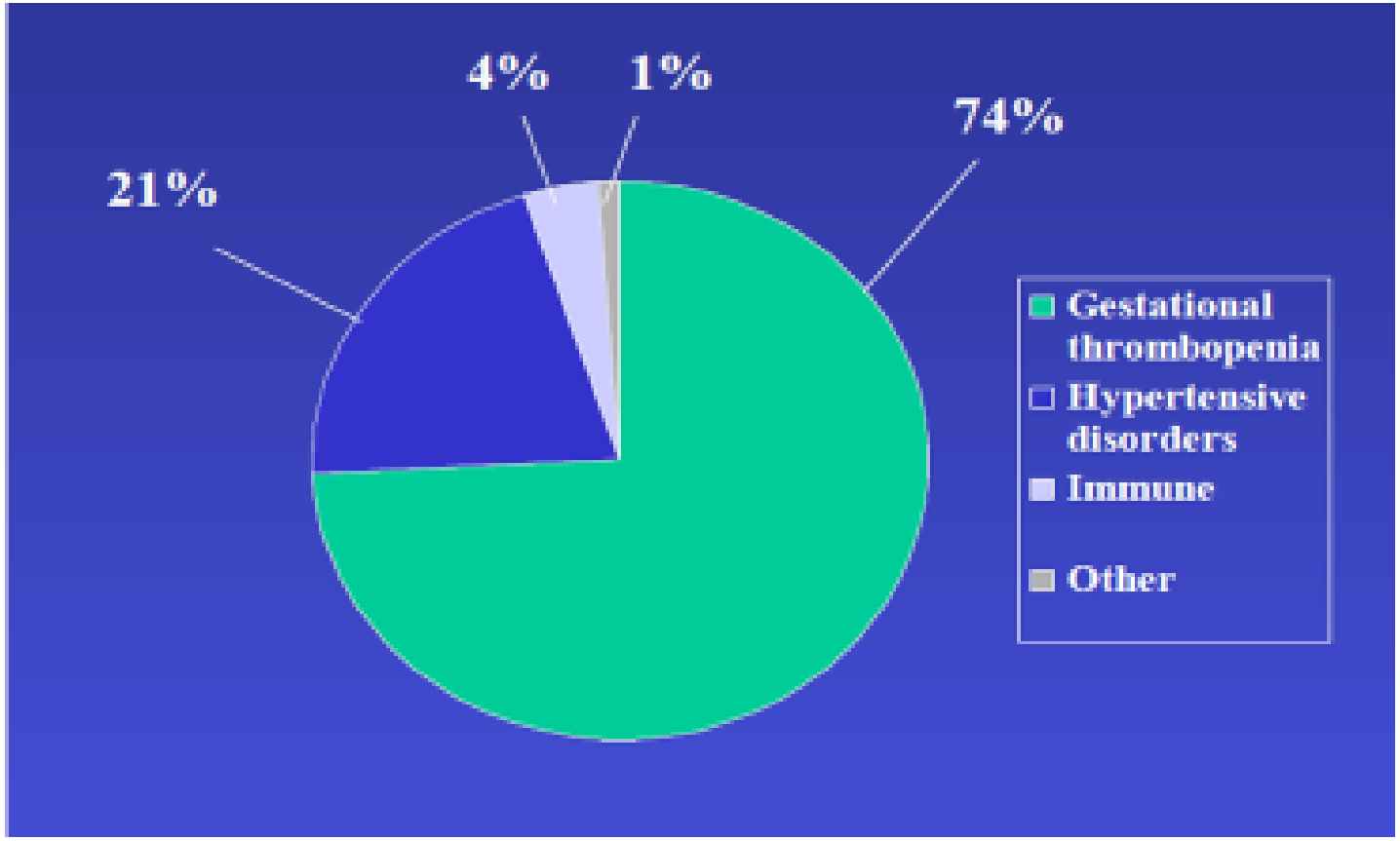


Figure 1. Thrombocytopenia in Pregnancy

Reference: Catherine Lambert,MD. Haematological disorders during pregnancy. Hemostatsis and Thrombosis Unit Division of Hematology Ciliques Universitaries Saint-Luc

CHANGES IN PLT COUNTS cont/

- Thrombocytopenia in pregnancy is a common reason for a haematologist consultation
- **The role of the haematologist is :**

1. Determine the cause
2. Advise in the management of thrombocytopenia
3. Help estimate the risk to the mother and foetus

Table 1. Differential diagnosis of Thrombocytopenia in Pregnancy

	Pregnancy- specific	**Not pregnancy-specific**
Isolated thrombocytopenia	Gestational thrombocytopenia (70-80%)	Primary ITP (1-4%) Secondary ITP (<1%)* Drug induced thrombocytopenia** Type IIB von Willebrand disease** Congenital thrombocytopenia**
Thrombocytopenia associated with systemic disorders	Severe pre-eclampsia (15-20%) HELLP syndrome (<1%) Acute fatty liver of pregnancy (<1%)	TTP/HUS** SLE** Antiphospholipid syndrome** Viral infections** Nutritional deficiency** Splenic sequestration(liver diseases, portal vein thrombosis, storage disease, etc)** Thyroid disorders**

*Secondary ITP – includes isolated thrombocytopenia secondary to some infections (HIV, HCV, H.pylori) and to other autoimmune disorders such as SLE.
**Rare (probably <1%)
Reference – American Society of Haematology. 2013 Clinical Practice Guide on Thrombocytopenia in Pregnancy.

Gestational Thrombocytopenia

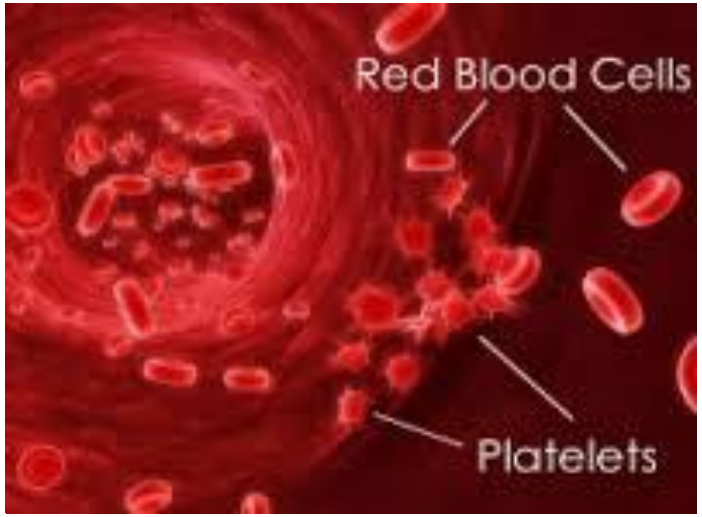
- Occurs in 5-9% of **healthy women**
- Mild-moderate thrombocytopenia (70-80x10^9/L)
- With about two-thirds being 130-150x10^9/L

Gestational Thrombocytopenia cont/

- Commonly occurs
  mid 2nd - 3rd trimester
- No maternal bleeding risk
- No foetal or neonatal thrombocytopenia or bleeding risk
- Normal platelet count outside of pregnancy and return to normal within 1- 2 months post partum

Gestational Thrombocytopenia cont/

- Is a diagnosis of exclusion
- The main competing diagnosis is ITP- considered if the degree of thrombocytopenia is more severe



Gestational Thrombocytopenia cont/

- Gestational thrombocytopenia VS ITP?
- No laboratory testing to differentiate the two
- Existence of pre-pregnancy thrombocytopenia should rule out GTP
- History of past pregnancies complicated by thrombocytopenia should favour gestational thrombocytopenia

Gestational Thrombocytopenia cont/

- Also response to immune modulation with steroids or immunoglobulins would favour ITP.

Gestational Thrombocytopenia cont/

- Treatment and Management:
- Not necessary if asymptomatic
- Platelet count monitoring recommended periodically, depending on the degree of thrombocytopenia
- Patients with platelet counts of 30-50x10^9/L should be able to deliver safely via NVD or surgically

The section below describes optimum management based on the different diagnoses of thrombocytopenia. <u>Read with CARE</u>

4. Gestational Thrombocytopenia

4.1 Presentation / Diagnosis:

- Usually mild to moderate; platelet count > $80x10^9$/L
- Incidental finding
- Diagnosis of exclusion
- No previous history
- No symptoms of bleeding
- Typically occurs in 3rd trimester
- Spontaneous resolution
- May recur in subsequent pregnancy

4.2 Management:

4.2.1 Antenatal:

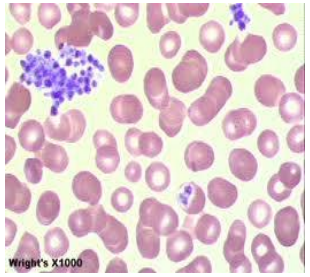
- **Refer for Consultant care**
- Exclude pathological causes
- Monitor platelet count every 4-6 weeks
- If moderate or severe: anaesthetic referral

4.2.2 Labour/Delivery:

- Avoid traumatic vaginal delivery to minimise maternal risk of haematoma formation
- Caesarean section for obstetric reasons only
- Epidural is safe if count above $80x10^9/L$
- If maternal count $<80x10^9/L$ – cord sample should be taken at delivery and neonatal count days 1 & 4

4.2.3 Postnatal:

- Verify that counts returns to normal after delivery



Laboratory Investigations

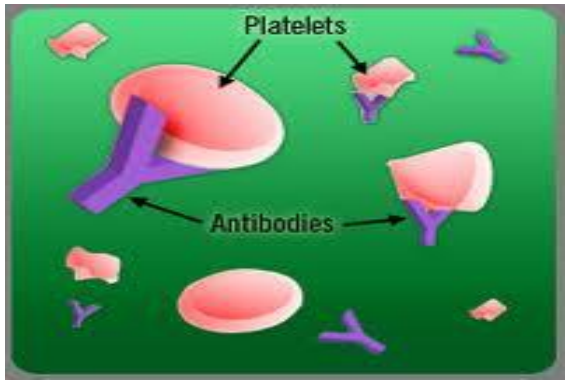
Recommended tests	Full blood count Reticulocyte count Peripheral blood smear Liver function tests Viral screening (HIV, HCV,HBV)
Tests to consider in clinically indicated	Antiphospholipid antibodies Antinuclear antibody (ANA) Thyroid function tests H.pylori testing DIC testing VWB type IIB testing* Coombs test^ Quantitative immunoglobulins^^
Tests that are not recommended	Antiplatelet antibody testing Bone marrow biopsy Thrombopoietin (TPO) levels

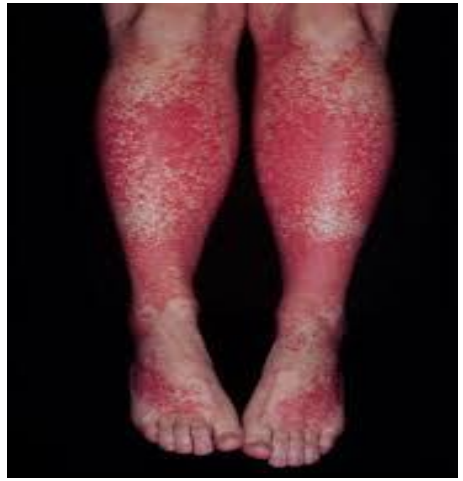
*Consider if history of bleeding, family history of thrombocytopenia, or unresponsive to ITP therapy
^ Appropriate to rule out autoimmune thrombocytopenia (Evans syndrome) if anaemia and reticulocytosis is present
^^In the setting of recurrent infections, low immunoglobulins may reveal a previously undiagnosed immunodeficiency disorder (e.g. common variable immune deficiency)

Reference – American Society of Haematology. 2013 Clinical Practice Guide on Thrombocytopenia in Pregnancy.

ITP In Pregnancy

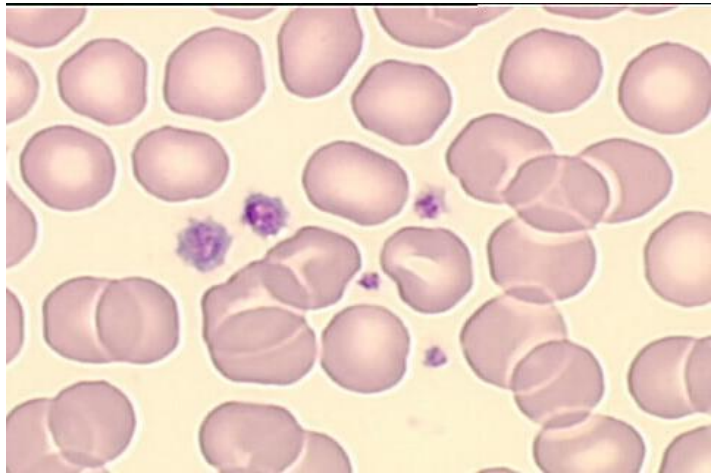
- The incidence is <1% accounting for 3% of all thrombocytopenic pregnancies
- Onset any trimester
- Thrombocytopenia outside of pregnancy
- Moderate thrombocytopenia <100x10^9/L but may be lower
- May have signs of bleeding, bruising, or petechiae



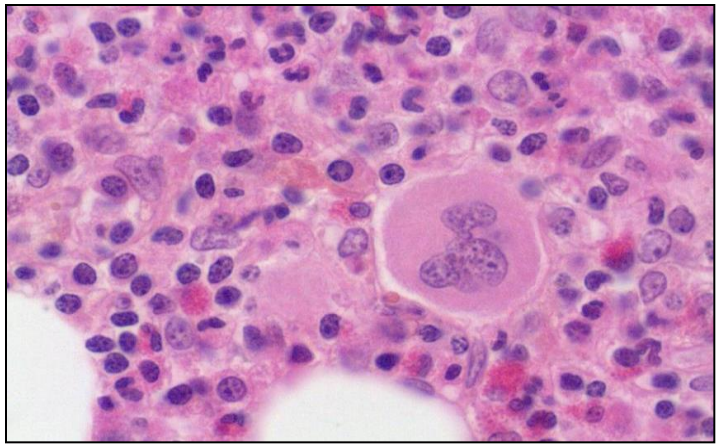


ITP in Pregnancy cont/

- +/- large platelets on peripheral blood smear



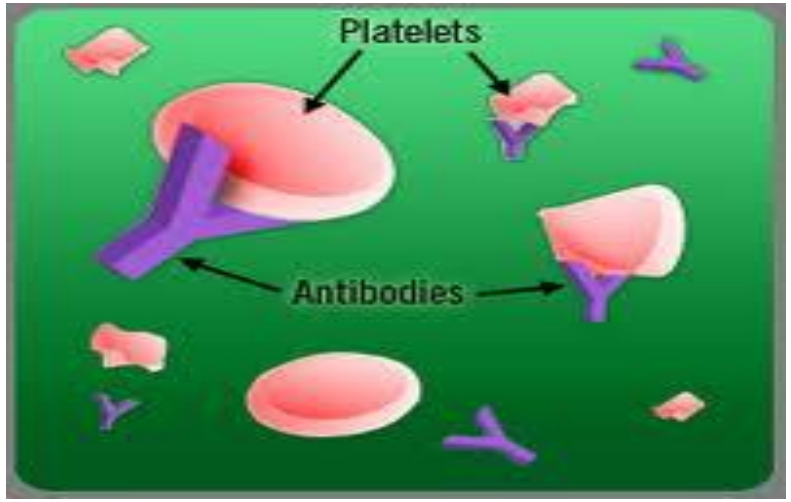
- Normal bone marrow biopsy



ITP in Pregnancy cont/

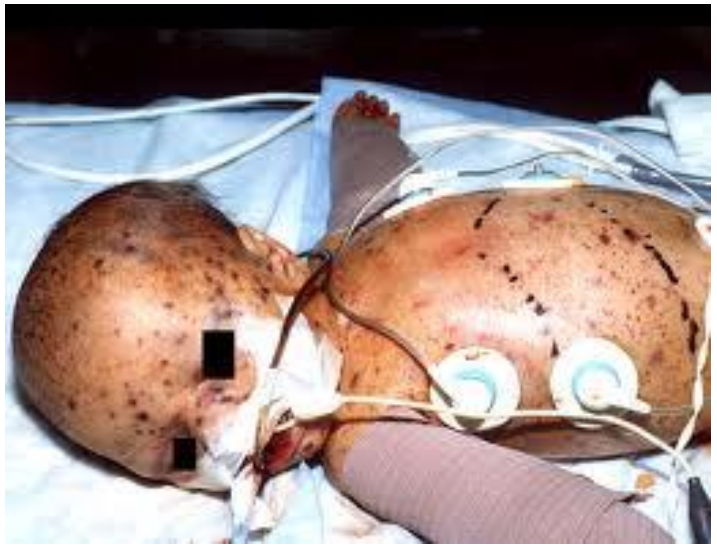
- Pathophysiology :

- Antibodies against platelet glycoproteins (GPIIb/IIIa and GPIb/IX leading to destruction in the RES)



ITP in Pregnancy cont/

- Is a diagnosis of exclusion
- May be associated with foetal thrombocytopenia – IgG antibodies cross the placenta
- However 90% of these neonates will not have significant thrombocytopenia



ITP in Pregnancy cont/

- Similarly to gestational thrombocytopenia there should be no additional haematological abnormalities, no microangiopathy, or evidence of DIC and liver dysfunction

Table 2. Therapeutic options for Management of ITP During Pregnancy

First line therapy	**Oral corticosteroids-initial response 2-14 days, peak response 4-28 days (C or D)** **IVIg-initial response 1-3 days, peak response 2-7 days (C)**
Second line therapy (For refractory ITP)	Combined corticosteroids and IVIg Splenectomy (2nd trimester)
Third line therapy	
Relatively contraindicated	Anti-D immunoglobulin (C) Azathioprine (D)**
Not recommended but use in pregnancy has been described	Cyclosporin A (C), Dapsone (C), TPO receptor agonists (C), Campath-1H (C), Rituximab (C)
Contraindicated	Cyclophosphamide (D), Vinca alkaloids (D), Danazol (X_

Table 2. cont/

^^^C = studies in animals show risk, but inadequate studies in human foetuses. Benefit may justify risk.

^^^D=Evidence of risk in human foetuses. Benefit may justify risk.

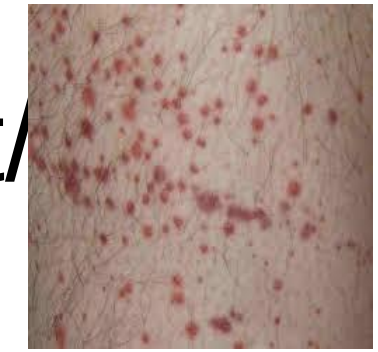
^^^X=Studies in animals or human foetuses demonstrate abnormalities Risk of harm outweigh benefits

** = used for other disorders during pregnancy

Reference for table 4:

2013 Clinical Practice Guide on Thrombocytopenia In pregnancy. American Society of haematology.

ITP in Pregnancy cont/



- Management at the time of delivery
- No need for treatment if no bleeding and platelet count ≥ 30x10^9/L - until 36 weeks of gestation
- If bleeding or platelet count <30x10^9/L – oral corticosteroids or IVI immunoglobulins
- The recommended starting dose for IVIg is 1g/kg

ITP in Pregnancy cont/

- Current recommendations - aim for a platelet count ≥ 50x10^9/L prior to labour and delivery as risk of caesarian section is present with every labour
- Platelet transfusion alone not effective in ITP – may be given in conjunction with IVIg if an adequate platelet count has not been achieved and delivery is emergent

ITP in Pregnancy cont/

- For a PLT <80x10^9/L in a patient who has not required steroids during pregnancy oral prednisone (or prednisolone) can be started 10 days before anticipated delivery at a dose of 10-20mg dly and titrated as necessary

5. Immune Thrombocytopenic Purpura (ITP)

5.1 Presentation / Diagnosis:

- May show: purpura, bruising, mucosal bleeding
- Asymptomatic
- Diagnosis of exclusion;
- Previous history;
- Platelet antibodies: lacks sensitivity and specificity
- Glycoprotein-specific antibodies
- Antibodies can cross placenta and cause fetal thrombocytopenia

5.2 Management:

5.2.1 Antenatal:

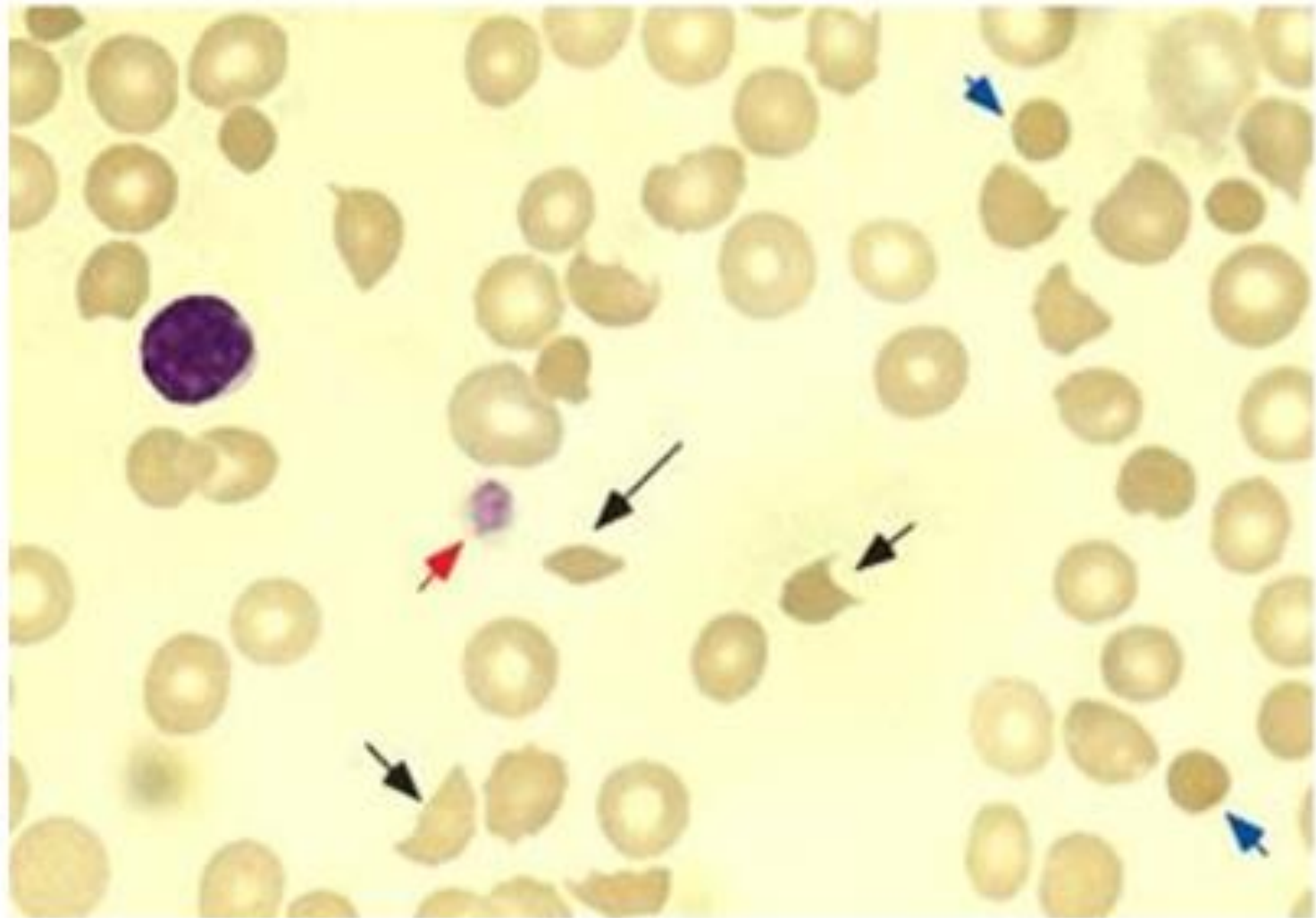
- Multidisciplinary care with Haematologist
- Optimize prior to pregnancy (azathioprine)
- Monitor platelet count
- Anaesthetic referral
- Treatment if symptoms or count $<20x10^9$/L at any stage of pregnancy or $<50x10^9$/L in late pregnancy without symptoms, consider, in consultation with Haematologist:
    1. Prednisolone 20 mg daily (start dose);
    2. iv IgG;
    3. Anti-D in Rh –positive women
    4. platelet transfusion
    5. Azathioprine

5.2.2 Labour/Delivery:

- Have platelets available if count <$50x10^9$/L (Discuss with consultant Obstetrician, Haematologist and Anaesthetist)
- In general, avoid epidural if count <$80x10^9$/L although a consultant anaesthetist may agree on a case by case basis
- Avoid traumatic delivery, fetal blood sampling (FBS), fetal scalp electrode (FSE)
- Caesarean section for obstetric reasons only
- Cord sample at delivery; Neonatal platelet count days 1 & 4

5.2.3 Postnatal:

- Platelet count daily until day 2-5
- If count <$20x10^9$/L or symptomatic – perform USS of brain and treat with iv IgG;
- Platelet transfusion if heavy bleeding



6. Thrombotic Thrombocytopenic Purpura (TTP)

6.1 Presentation / Diagnosis:

Life-threatening disorder with five of signs due to a severe deficiency of vW's factor-cleaving protein:

- microangiopatic haemolytic anaemia
- thrombocytopenia
- neurological symptoms (from headache to coma)
- renal dysfunction;
- fever

6.2 Diagnosis:

- ADAMTS13 levels;
- Low platelet count,
- Abnormal U&E

6.3 Management:

- Multidisciplinary management with Haematologist
- Urgent plasma exchange may be required until platelet count is normal;
- High doses of steroids
- Platelet transfusion – CONTRAINDICATED
- Anaesthetic involvement
- Central line
- Delivery does not improve outcome unless poor response to treatment

7. Haemolytic Uraemic Syndrome (HUS)

7.1 Presentation / Diagnosis:

- Associated with *E.coli* infection
- Microangiopatic haemolytic anaemia
- Thrombocytopenia
- Renal involvement
- Often postpartum

7.2 Management:

- Supportive management
- Renal dialysis
- Red cell transfusion
- Caesarean section for obstetric reasons

8. Drug induced

8.1 Diagnosis:

- History of the use of the drug (heparin)

8.2 Management:

- Stop use of the drug
- Use the alternative for Heparin – Danaparoid;
- Check platelet count weekly for the first 3 weeks after commencin heparin in pregnancy.

A 22-year-old woman from Sudan is found to have a platelet count of 82 109/L on routine screening at 16 weeks' gestation of her second pregnancy. Her first child was delivered at term without complications. She was told her platelet count was 62 109/L

. She has no knowledge of blood counts done at any other time. Her mother had the last of her 8 pregnancies (all uncomplicated) 2 years earlier and was found to have a low platelet count.
The patient denies any history of bleeding or bruising. Her history and examination are otherwise unremarkable.

What are the most probable etiologies of her thrombocytopenia?

Table 1. Causes and relative incidence of thrombocytopenia in pregnancy

Pregnancy-specific
Isolated thrombocytopenia
Gestational thrombocytopenia (70%-80%)
Thrombocytopenia associated with systemic disorders
Preeclampsia (15%-20%)
HELLP syndrome (< 1%)
Acute fatty liver of pregnancy (< 1%)
Not pregnancy-specific
Isolated thrombocytopenia
Primary immune thrombocytopenia–ITP (1%-4%)
Secondary ITP (< 1%)*
Drug-induced thrombocytopenia (< 1%)
Type IIb VWD (< 1%)
Congenital (< 1%)
Thrombocytopenia associated with systemic disorders
TTP/HUS (< 1%)
SLE (< 1%)
Antiphospholipid antibody syndrome (< 1%)
Viral infections (< 1%)
Bone marrow disorders (< 1%)
Nutritional deficiency (< 1%)
Splenic sequestration (liver diseases, portal vein thrombosis, storage disease, etc; < 1%)

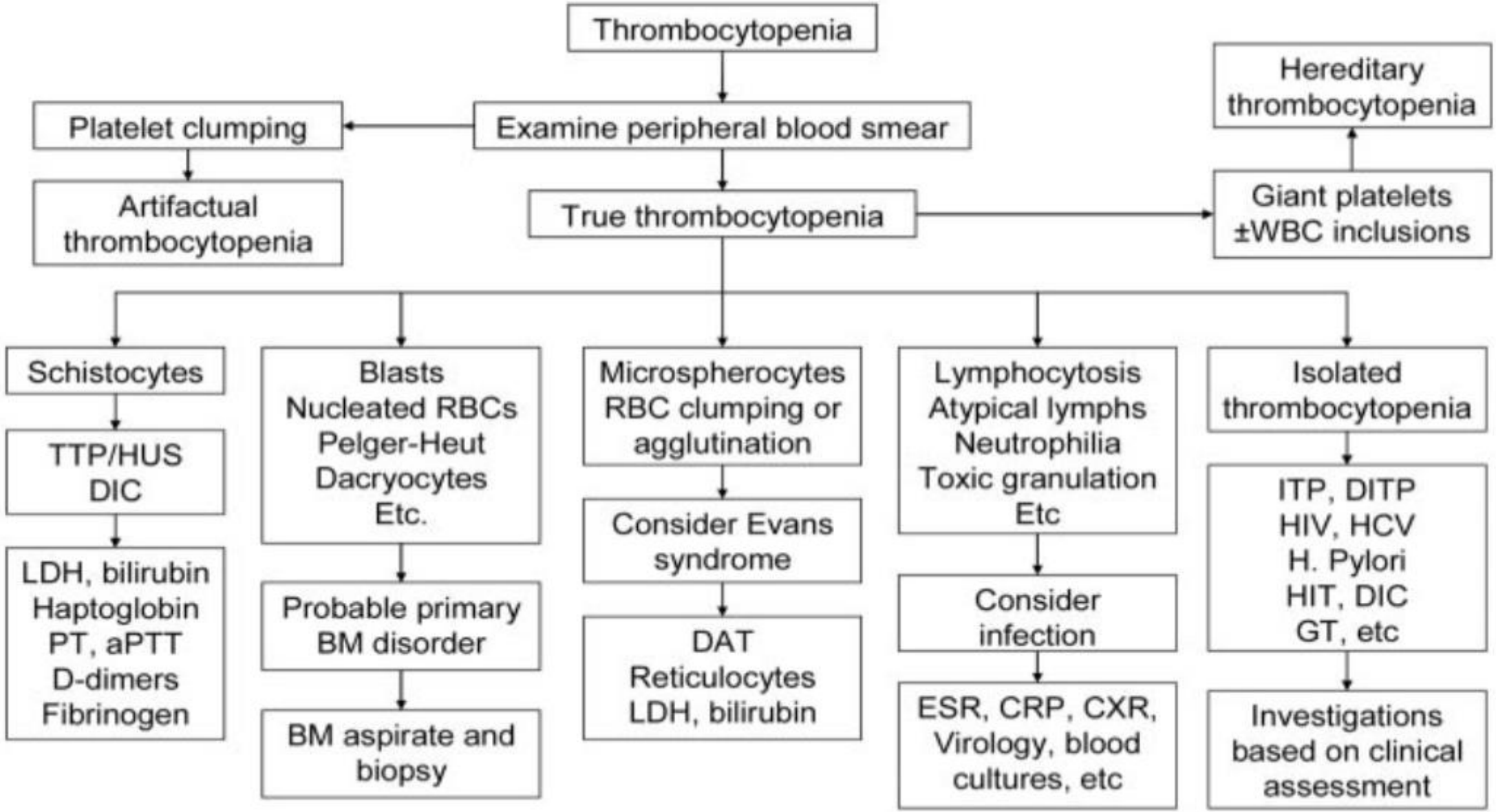
*Secondary ITP includes isolated thrombocytopenia secondary to some infections (HIV, HCV, *H pylori*) and to other autoimmune disorders, such as SLE.

What testing should be ordered when a patient presents with thrombocytopenia during pregnancy?

Table 3. Basic laboratory evaluation of pregnant women with isolated thrombocytopenia

Complete blood count and reticulocyte count
Peripheral blood film
Liver function tests
Thyroid function tests
Quantitative immunoglobulin level measurement
Direct antiglobulin test
Antiphospholipid antibodies
ANA
H pylori
HIV
HCV
HBV
VWD type IIB testing*

How often should the patient be monitored and what will be the indication for treatment of thrombocytopenia?


Thrombocytopenia
Examine peripheral blood smear
Platelet clumping
Artifactual thrombocytopenia
True thrombocytopenia
Hereditary thrombocytopenia
Giant platelets ±WBC inclusions
Schistocytes
TTP/HUS DIC
LDH, bilirubin Haptoglobin PT, aPTT D-dimers Fibrinogen
Blasts Nucleated RBCs Pelger-Heut Dacryocytes Etc.
Probable primary BM disorder
BM aspirate and biopsy
Microspherocytes RBC clumping or agglutination
Consider Evans syndrome
DAT Reticulocytes LDH, bilirubin
Lymphocytosis Atypical lymphs Neutrophilia Toxic granulation Etc
Consider infection
ESR, CRP, CXR, Virology, blood cultures, etc
Isolated thrombocytopenia
ITP, DITP HIV, HCV H. Pylori HIT, DIC GT, etc
Investigations based on clinical assessment

Management of ITP in pregnancy

Case 2

A 36-year-old woman, gravida 2 para 2 (G2P2), with a history of ITP since age 28 asks whether she can safely become pregnant again.

Her platelet count is typically 40-60 109/L but can fall lower after upper respiratory tract infections or at times of physical stress.

She has been treated with and responded to corticosteroids and IVIg in the past. Her last pregnancy was complicated by a platelet count of 20 109/L in her third trimester requiring both corticosteroids and IVIg. The platelet count was 90 109/L at term, and she delivered a healthy neonate with a platelet count of 125 109/L.

What can the patient expect during a subsequent pregnancy?

What treatments are safe during pregnancy?

Table 4. Therapeutic options for ITP in pregnancy

First-line therapy	Intravenous gammaglobulin (IVIg) oral corticosteroids
Second line*	Combination therapy with corticosteroids and IVIg
	Splenectomy (second trimester)
Other therapeutic options†	
Relatively contraindicated	Anti-D immunoglobulin [C]
	Azathioprine [D]
Not recommended but use in pregnancy described	Cyclosporine A [C]
	Dapsone [C]
	Thrombopoietin receptor agonists [C]‡
	Campath-1H [C]
	Rituximab [C]
Contraindicated	Mycophenolate mofetil [C]
	Cyclophosphamide [D]
	Vinca alkaloids [D]
	Danazol [X]

*For refractory thrombocytopenia or poorly tolerated side effects.

†FDA designated pregnancy category in brackets.

‡As reported on the official package inserts (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm), although no studies have been published.

How should delivery be managed? What is a safe platelet count for epidural anesthesia?

What is the risk to the neonate?

How should he be monitored?

Thrombotic microangiopathies of pregnancy

Preeclampsia, the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets), and acute fatty liver of pregnancy (AFLP) have overlapping clinical and laboratory features with thrombotic microangiopathies that are not specific to pregnancy and may pose considerable diagnostic challenges

Case 3

A 38-year-old gravida 2 para 0 woman at 39 weeks' gestation presented to the obstetric unit after a tonic-clonic seizure witnessed by her husband. Abnormal laboratory findings included: Hb14.7 g/dL, WBC 15.3 109/L, platelets 87 109/L, albumin 25 g/L. The urine dipstick revealed significant proteinuria .

Transaminases and lactic dehydrogenase (LDH) were not determined because of a hemolyzed blood sample. Coagulation results and creatinine were normal. The blood film confirmed true thrombocytopenia, with some giant platelets and a few red cell fragments.

What is the most probable etiology of her thrombocytopenia?

How can we explain her clinical deterioration and worsening thrombocytopenia

What is the standard management of thrombotic microangiopathies of pregnancy?

Case 4

A 28-year-old primigravida at 18 weeks' gestation presented to the emergency department with a 1-week history of worsening fatigue, shortness of breath, nausea, abdominal pain, and easy bruising. On examination, the patient was pale, tachycardic, and had a few ecchymoses on her legs. Her blood count showed Hb 7.3 g/dL, WBC 12.4 109/L, platelets 27 109/L. Other abnormal laboratory tests included bilirubin 31M and LDH 873 U/L. Renal function tests were normal. The peripheral blood film revealed a
true thrombocytopenia with the presence of several large platelets, 10-20 red cell fragments per high power field, scattered spherocytes, and occasional nucleated red cells; polychromasia was increased.

What is the most probable etiology of the thrombocytopenia?

What is the management of TTP/HUS in pregnancy?

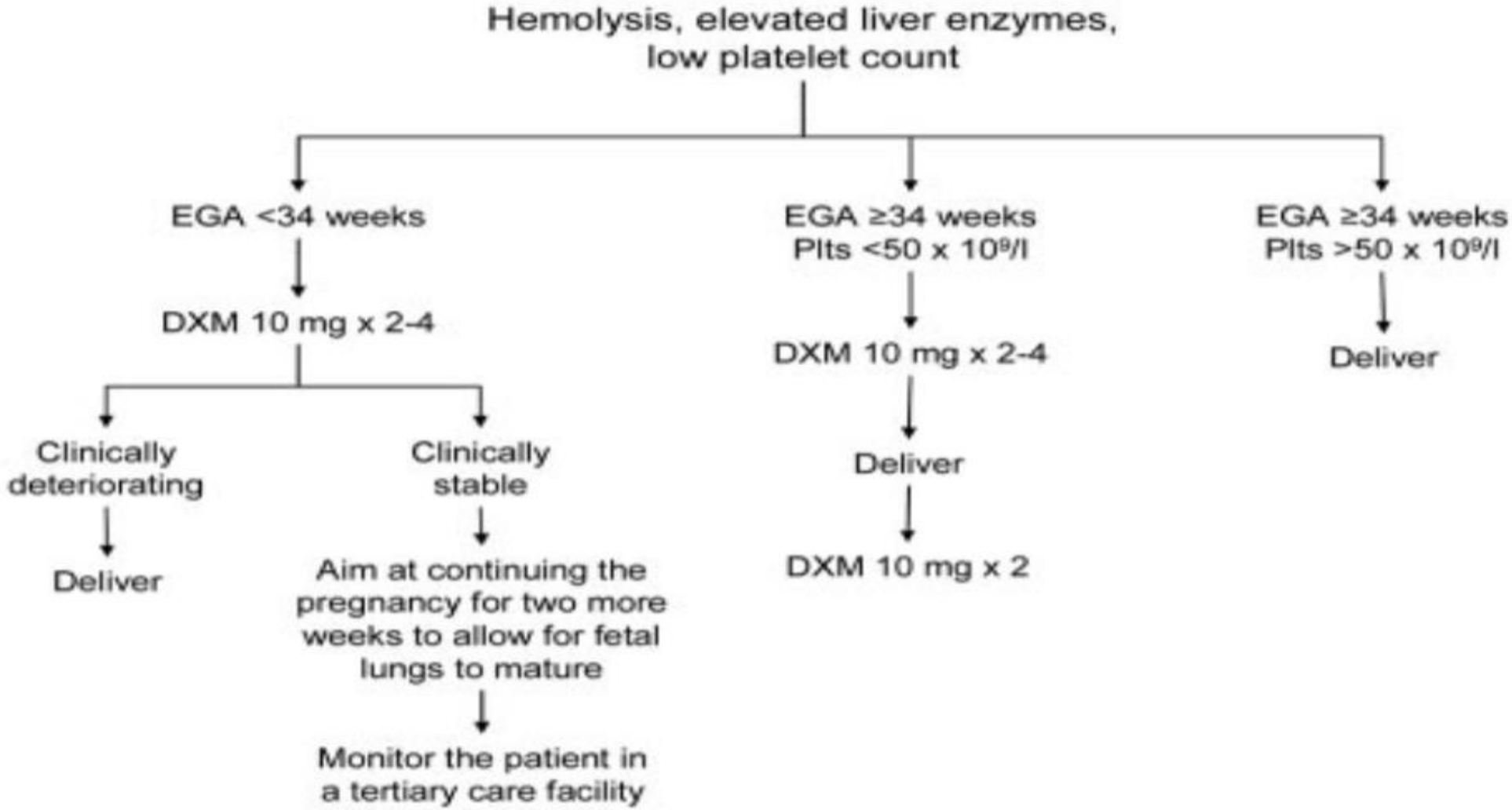


Figure 2. Suggested approach to the management of patients with HELLP syndrome. EGA indicates estimated gestational age.

THANK YOU