CancerCare Manitoba
ActionCancerManitoba

FOR Health Professionals

Hematologic Disorders in Pregnancy: What to expect when you're expecting

Chantalle Menard – MD FRCPC (PGY-5)
Arjuna Ponnampalam - MD FRCPC

University of Manitoba

CancerCare Manitoba
COMMUNITY ONCOLOGY PROGRAM

Presenter Disclosure

- **Faculty / Speaker's name:** Chantalle Menard & Arjuna Ponnampalam

- **Relationships with commercial interests:**
  - **Grants/Research Support:** None
  - **Speakers Bureau/Honoraria:** None
  - **Consulting Fees:** None
  - **Other:** None

Mitigating Potential Bias

- Not applicable

Learning Objectives

1. Recognize expected physiologic changes in hematologic parameters with pregnancy
2. Identify causes of thrombocytopenia and anemia in pregnancy.
3. Know when referral is necessary based on information provided by the CBC

Hematological Changes in Pregnancy

- Plasma volume expands 40-60%
  - Red blood cell mass expands by only 20-50% → physiologic anemia develops (hematocrit 30-32%)
  - Hemoglobin levels typically >110 g/L.
- Prevalence of anemia increases in each trimester
  - 8% → 12% → 34%

Hematological Changes in Pregnancy

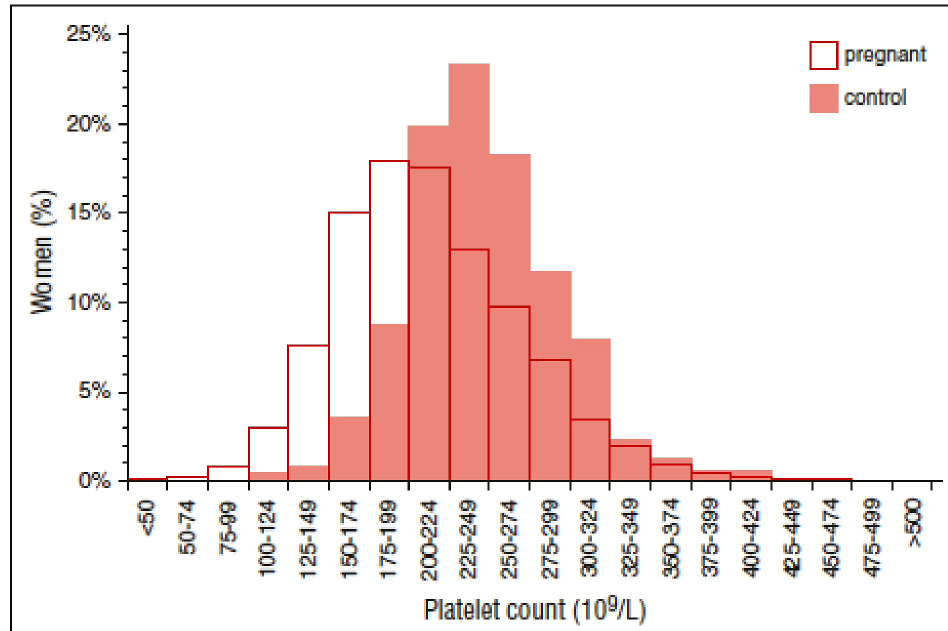


Figure 2. Distribution of platelet counts in healthy pregnant women at term. Reprinted from Boehlen et al[10] with permission.

Cines & Levine. *Thrombocytopenia in Pregnancy.* ASH Education. 2017

Hematological Changes in Pregnancy

- White blood cell count increases (leukocytosis)
  - Predominantly neutrophilia
- Occurs due to increased drive of hematopoiesis under physiologic stress
- Monocyte count increases
  - Particularly in the first trimester

Case 1

- 32 year old female, G2P1 at 28 weeks
- Routine bloodwork:

Test	Value	Ref Range
WBC	12×10^9/L	4.5-11.0 $\times 10^9$/L
Hemoglobin	115 g/L	120 – 160 g/L
MCV	88 fL	80– 98 fL
Platelets	98×10^9/L	140 – 440 $\times 10^9$/L

Case 2

- 32 year old female, G2P1 at 32 weeks
- Diagnosed with preeclampsia at 28 weeks
- Complains of RUQ pain

Test	Value	Ref Range
WBC	12 x 10^9/L	4.5-11.0 x 10^9/L
Hemoglobin	83 g/L	120 – 160 g/L
MCV	88 fL	80– 98 fL
Platelets	45 x 10^9/L	140 – 440 x 10^9/L

Case 3

- 32 year old female, G2P1 at 8 weeks
- Routine bloodwork:

Test	Value	Ref Range
WBC	10.6 x 10^9/L	4.5-11.0 x 10^9/L
Hemoglobin	123 g/L	120 – 160 g/L
MCV	88 fL	80– 98 fL
Platelets	62 x 10^9/L	140 – 440 x 10^9/L

Thrombocytopenia in Pregnancy

	Pregnancy-specific	Not pregnancy specific
Isolated thrombocytopenia	Gestational Thrombocytopenia (70-80%)	Primary ITP (1-4%) Secondary ITP (<1%) Drug-induced thrombocytopenia (<1%) Congenital thrombocytopenia (<1%)
Thrombocytopenia associated with systemic disorders	Severe preeclampsia (15-20%) HELLP syndrome (<1%) AFLP (<1%)	TTP/HUS (<1%) SLE (<1%) Antiphospholipid syndrome (<1%) Viral infections (<1%) Bone marrow disorders (<1%) Nutritional deficiencies (<1%) Splenic sequestration (<1%) Thyroid disorders (<1%)

Adapted from Gernsheimer T, James AH, Stasi R. How I treat thrombocytopenia in pregnancy. *Blood*. 2013; 121(1):38-47.

Gestational Thrombocytopenia

- 5% of all pregnancies
- 75% of all cases of thrombocytopenia in pregnancy
- Mid-second to third trimester
- Platelet counts typically 70 – 149 $x10^9/L$
  - Only 1-5% develop counts <100 $x10^9/L$
- No adverse health consequences to the fetus or the mother
  - May affect candidacy for neuro-axial anesthesia

Cines & Levine. *Thrombocytopenia in Pregnancy.* ASH Education. 2017
The American College of Obstetrians & Gynecologists. *Thrombocytopenia in pregnancy.* Obs. & Gyn. 2016:128(3).

Gestational Thrombocytopenia

- Treatment
  - No therapy is recommended
  - Resolves 1-2 months post-partum
    - Confirm with CBC
  - Monitor at antepartum visits
  - May (or may not) recur with subsequent pregnancies

Cines & Levine. *Thrombocytopenia in Pregnancy.* ASH Education. 2017
The American College of Obstetrians & Gynecologists. *Thrombocytopenia in pregnancy.* Obs. & Gyn. 2016:128(3).

Preeclampsia

- New onset of hypertension ≥20 weeks gestation with proteinuria
- 15-20% of thrombocytopenia in pregnancy
- Severe cases may be accompanied by:
  - Thrombocytopenia $\leq 100 \times 10^9$/L
  - Impaired liver function
  - New onset renal impairment
  - Pulmonary edema
  - New onset cerebral or visual disturbance

Cines & Levine. *Thrombocytopenia in Pregnancy.* ASH Education. 2017
The American College of Obstetrians & Gynecologists. *Thrombocytopenia in pregnancy.* Obs. & Gyn. 2016:128(3).

Preeclampsia

- Treatment:
  - Urgent referral to obstetrics
  - Expedient delivery of the fetus (if severe)

Cines & Levine. *Thrombocytopenia in Pregnancy.* ASH Education. 2017.
Gernsheimer et al. *How I treat thrombocytopenia in pregnancy.* Blood; 121 (1).

HELLP Syndrome

- Hemolysis, Elevated Liver Enzymes, Low Platelets
- Occurs with (80%) and without (20%) preeclampsia
- <1% of all thrombocytopenia in pregnancy

Cines & Levine. *Thrombocytopenia in Pregnancy.* ASH Education. 2017.
Gernsheimer et al. *How I treat thrombocytopenia in pregnancy.* Blood; 121 (1).

HELLP Syndrome

- Diagnosis:
  - 28-36 weeks of gestation
  - Hemolysis
    - Schistocytes, Elevated bilirubin & LDH, low haptoglobin
  - Liver enzyme elevation
  - Thrombocytopenia (often $<50 \times 10^9$/L)
- Can be difficult to differentiate from TTP!!

Cines & Levine. *Thrombocytopenia in Pregnancy.* ASH Education. 2017.
Gernsheimer et al. *How I treat thrombocytopenia in pregnancy.* Blood; 121 (1).

HELLP Syndrome

- Treatment:
  - Urgent referral to obstetrics
  - Transfer to tertiary care center
  - Expedient delivery of the fetus

Cines & Levine. *Thrombocytopenia in Pregnancy.* ASH Education. 2017.
Gernsheimer et al. *How I treat thrombocytopenia in pregnancy.* Blood; 121 (1).

Acute Fatty Liver of Pregnancy (AFLP)

- Third trimester
- Can overlap with symptoms of HELLP and severe preeclampsia
- <1% of all thrombocytopenia in pregnancy

Cines & Levine. *Thrombocytopenia in Pregnancy.* ASH Education. 2017.
Gernsheimer et al. *How I treat thrombocytopenia in pregnancy.* Blood; 121 (1).

Acute Fatty Liver of Pregnancy (AFLP)

- Clinical Features:
  - Severe thrombocytopenia (<20x10^9/L)
  - Evidence of disseminated intravascular coagulation
    - Elevated INR
    - Bleeding
  - Liver transaminases >1000 IU/L
  - Elevated bilirubin
  - Hypoglycemia

Cines & Levine. *Thrombocytopenia in Pregnancy.* ASH Education. 2017.
Gernsheimer et al. *How I treat thrombocytopenia in pregnancy.* Blood; 121 (1).

Acute Fatty Liver of Pregnancy (AFLP)

- Treatment:
  - Urgent referral to obstetrics
  - Transfer to tertiary care center
  - Expedient delivery of the fetus

Cines & Levine. *Thrombocytopenia in Pregnancy.* ASH Education. 2017.
Gernsheimer et al. *How I treat thrombocytopenia in pregnancy.* Blood; 121 (1).

Immune Thrombocytopenia (ITP)

- 1-4% of all pregnancies
- 3% of thrombocytopenia in pregnancy
  - Most common cause of a platelet count <50 x 10^9/L
- Suspect when otherwise healthy woman develops platelets <70 x10^9/L at any point in pregnancy, or thrombocytopenia in the first trimester.

Cines & Levine. *Thrombocytopenia in Pregnancy.* ASH Education. 2017.
Gernsheimer et al. *How I treat thrombocytopenia in pregnancy.* Blood; 121 (1).

Immune Thrombocytopenia (ITP)

- Management
  - Treatment not indicated unless bleeding, or platelets <30 $x10^9/L$
  - Refer to Hematology if requiring treatment
  - If counts stable, monitor platelet counts monthly, and then weekly once 32-34 weeks

Cines & Levine. *Thrombocytopenia in Pregnancy.* ASH Education. 2017.
Gernsheimer et al. *How I treat thrombocytopenia in pregnancy.* Blood; 121 (1).
The American College of Obstetrians & Gynecologists. *Thrombocytopenia in pregnancy.* Obs. & Gyn. 2016:128(3).

Immune Thrombocytopenia (ITP)

- Management (continued)
  - May need treatment prior to neuro-axial anesthesia
  - Newborn should be monitored for thrombocytopenia at delivery, and 4-7 days post delivery

Common Causes of Anemia in Pregnancy

1. Iron deficiency
2. Iron deficiency
3. Iron deficiency

- 75% of all cases of non-physiologic anemia in pregnancy
  - Ferritin <20 ng/mL = diagnostic
  - Ferritin 20-50 ng/mL = probable
  - Ferritin >50 ng/mL = unlikely*
- Supplementation of oral iron (15-30mg/day) recommended

Less Common Causes of Anemia in Pregnancy

Pregnancy-specific	Not pregnancy specific
HELLP AFLP Severe preeclampsia	Megaloblastic anemia Thalassemia Sickle cell disease Bone marrow failure disorders Bone marrow infiltrative disorders TTP/HUS

ANEMIA

STEP 1

WBC OR PLATELETS ALSO ABNORMAL?

YES → **MULTIPLE CYTOPENIAS**

- Blood Smear
  - Schistocytes → TTP/HUS
  - Blasts, NRBCs, Dysplasia, Immature WBCs → Bone Marrow → Marrow Infiltration, Myelodysplasia, Acute Leukemia
  - Smear normal and other cytopenias not severe → STEP 2

NO → **STEP 2**

MCV

NORMOCYTIC

STEP 3

RETICULOCYTE COUNT

MICROCYTIC

- Ferritin
  - Low → Iron Deficiency
  - Normal, with signs of inflammation → Consider trial of iron therapy → Iron Deficiency
  - Consider trial of iron therapy → Active Inflammation? If needed check ESR, CRP
  - High → Active Inflammation? If needed check ESR, CRP → Chronic Disease*
  - Active Inflammation? → Hb Electrophoresis → Thalassemia

GENETICS CONSULTATION SUGGESTED

STEP 3A

- Acute blood loss or hemolyisis
- Normal or Low → **HYPOPROLIFERATIVE**
  - Drug History → Marrow Toxin
  - Creatinine → Renal Failure
  - Active inflammation? ESR, CRP → Chronic Disease*
  - Ferritin, B12 → Combined Anemia
  - LFTs & Enzymes → Liver Disease**
  - Endocrine Tests → Hypothyroidism Testerone**
  - SPEP & FLCR → Myeloma
  - Bone Marrow → Marrow Infiltration; Stem Cell Defect
  - Blood Smear → Combined Anemia, Liver Disease**, Hypothyroidism Testerone**, Myeloma, Marrow Infiltration
- High → **HYPERPROLIFERATIVE**

STEP 3B

- LDH, bilirun, haptoglobin
  - Normal → Recovery from nutient deficiency toxic exposure, or acute blood loss
  - Abnormal → **Hemolytic** → Blood Smear
    - **Schistocytes** → Microangiopathic or Mechanical
    - **Spherocytes** → Coombs Test
    - **Normal** → Coombs Test
    - Coombs Test → Spherocytosis; Autoimmune
    - G-6-PD, PK Screen → Enzymopathy

MACROCYTIC

- Serum B12 → B12 Deficiency
- Retic. Count → High → HYPERPROLIFERATIVE
- Medication and Alcohol History → Antimetabolites, Alcoholism*; Potential Folate Deficiency
- LFTs & Enzymes → Liver Disease*
- Bone Marrow → Myelodysplasia*

* Alteration in MCV is generally modest, and MCV is often within normal range

** Uncommon to cause more than mild anemia; test according to clinical context

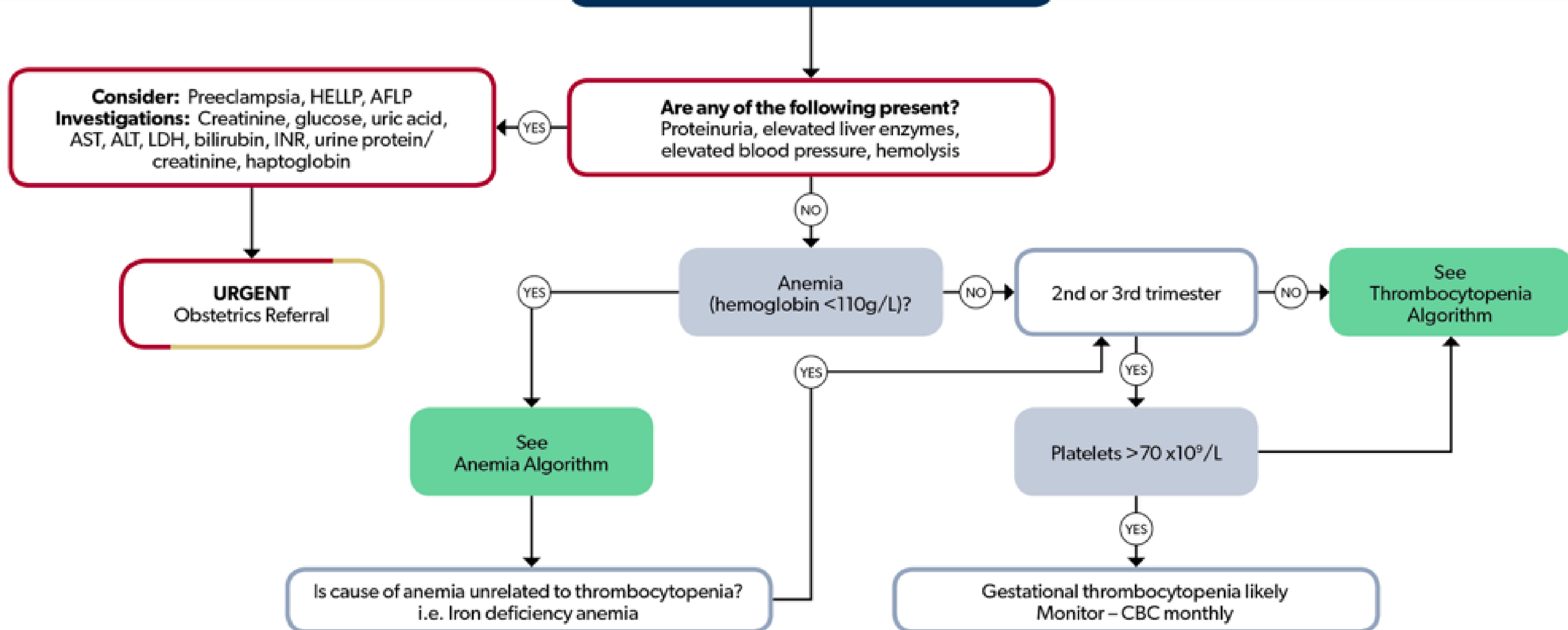
GRAY AREA:
HEMATOLOGY CONSULTATION RECOMMENDED

© Donald S. Houston MD 2016

Case 1

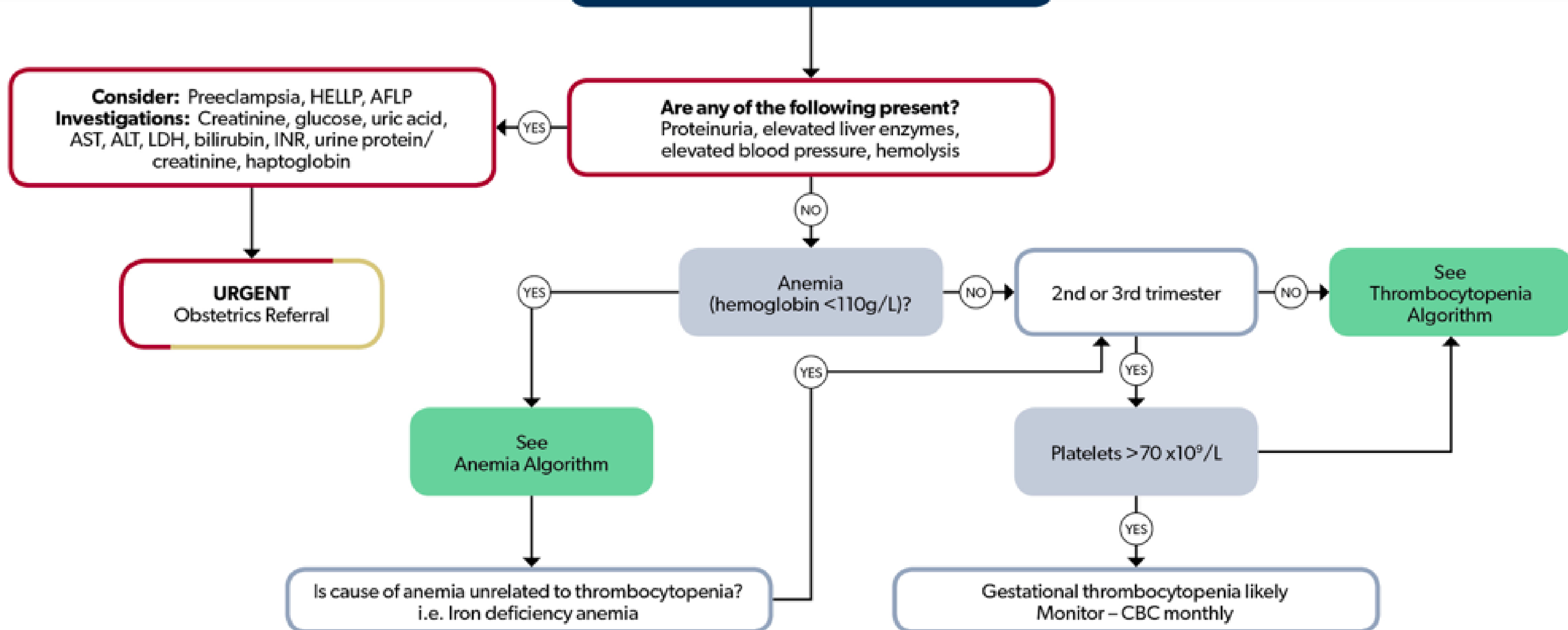
- 32 year old female, G2P1 at 28 weeks
- Routine bloodwork:

Test	Value	Ref Range
WBC	12 x 10^9/L	4.5-11.0 x 10^9/L
Hemoglobin	115 g/L	120 – 160 g/L
MCV	88 fL	80– 98 fL
Platelets	98 x 10^9/L	140 – 440 x 10^9/L


Thrombocytopenia in Pregnancy
(Platelets <130 x10⁹/L)
Are any of the following present?
Proteinuria, elevated liver enzymes, elevated blood pressure, hemolysis
YES
Consider: Preeclampsia, HELLP, AFLP
Investigations: Creatinine, glucose, uric acid, AST, ALT, LDH, bilirubin, INR, urine protein/creatinine, haptoglobin
URGENT
Obstetrics Referral
NO
Anemia
(hemoglobin <110g/L)?
YES
See
Anemia Algorithm
Is cause of anemia unrelated to thrombocytopenia?
i.e. Iron deficiency anemia
YES
NO
2nd or 3rd trimester
NO
See
Thrombocytopenia
Algorithm
YES
Platelets >70 x10⁹/L
YES
Gestational thrombocytopenia likely
Monitor – CBC monthly

Case 1

Test	Value	Ref. Range
Blood Pressure	110/75	<140/90
Creatinine	52 µmol/L	50 – 90 µmol/L
LDH	175 U/L	90 – 230 U/L
Total Bilirubin	16 µmol/L	<26 µmol/L
Haptoglobin	1.4 g/L	0.3 – 2.0 g/L
ALT	23 U/L	5 – 32 U/L
Urinalysis	Protein Negative	Negative

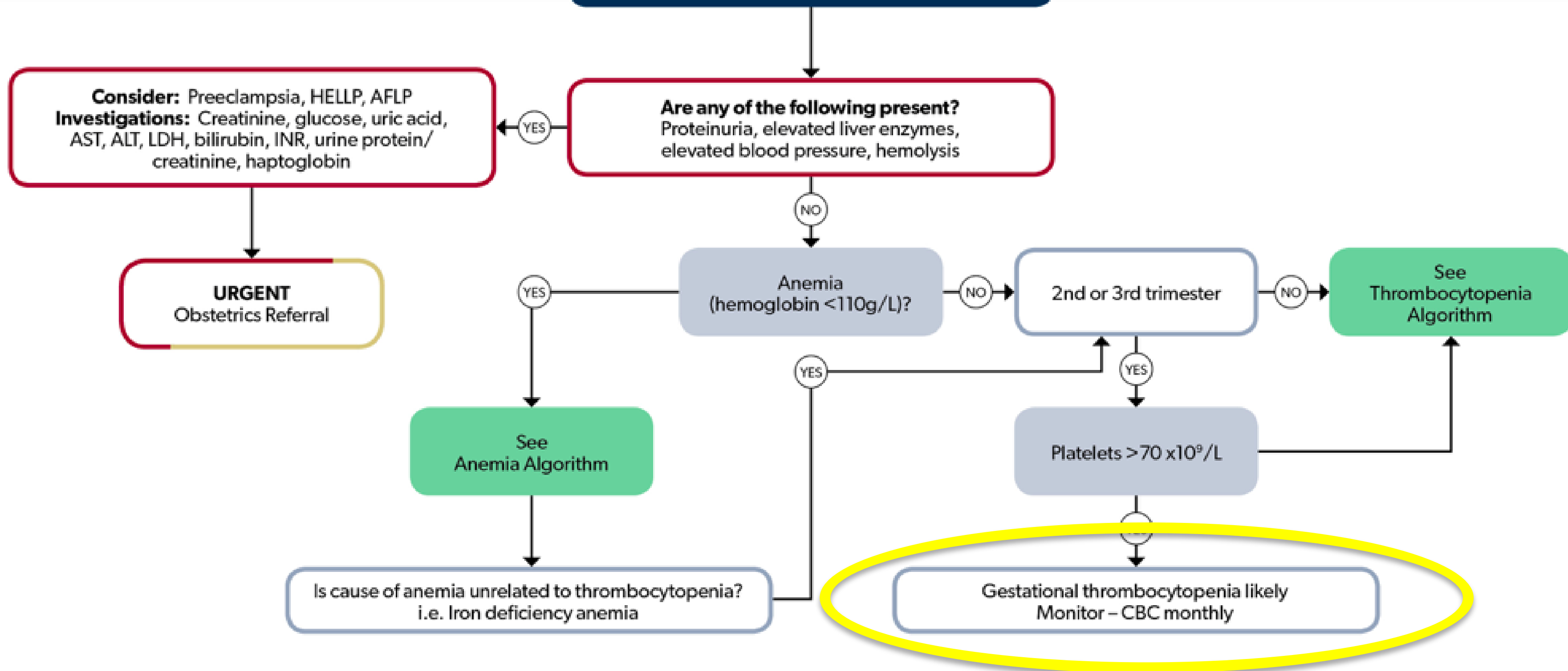


Thrombocytopenia in Pregnancy
(Platelets <130 x10⁹/L)
Are any of the following present?
Proteinuria, elevated liver enzymes, elevated blood pressure, hemolysis
YES
Consider: Preeclampsia, HELLP, AFLP
Investigations: Creatinine, glucose, uric acid, AST, ALT, LDH, bilirubin, INR, urine protein/creatinine, haptoglobin
URGENT
Obstetrics Referral
NO
Anemia
(hemoglobin <110g/L)?
YES
See
Anemia Algorithm
Is cause of anemia unrelated to thrombocytopenia?
i.e. Iron deficiency anemia
YES
NO
2nd or 3rd trimester
NO
See
Thrombocytopenia Algorithm
YES
Platelets >70 x10⁹/L
YES
Gestational thrombocytopenia likely
Monitor – CBC monthly

Case 1

- 32 year old female, G2P1 at 28 weeks
- Routine bloodwork:

Test	Value	Ref Range
WBC	12 x 10^9/L	4.5-11.0 x 10^9/L
Hemoglobin	115 g/L	120 – 160 g/L
MCV	88 fL	80– 98 fL
Platelets	98 x 10^9/L	140 – 440 x 10^9/L

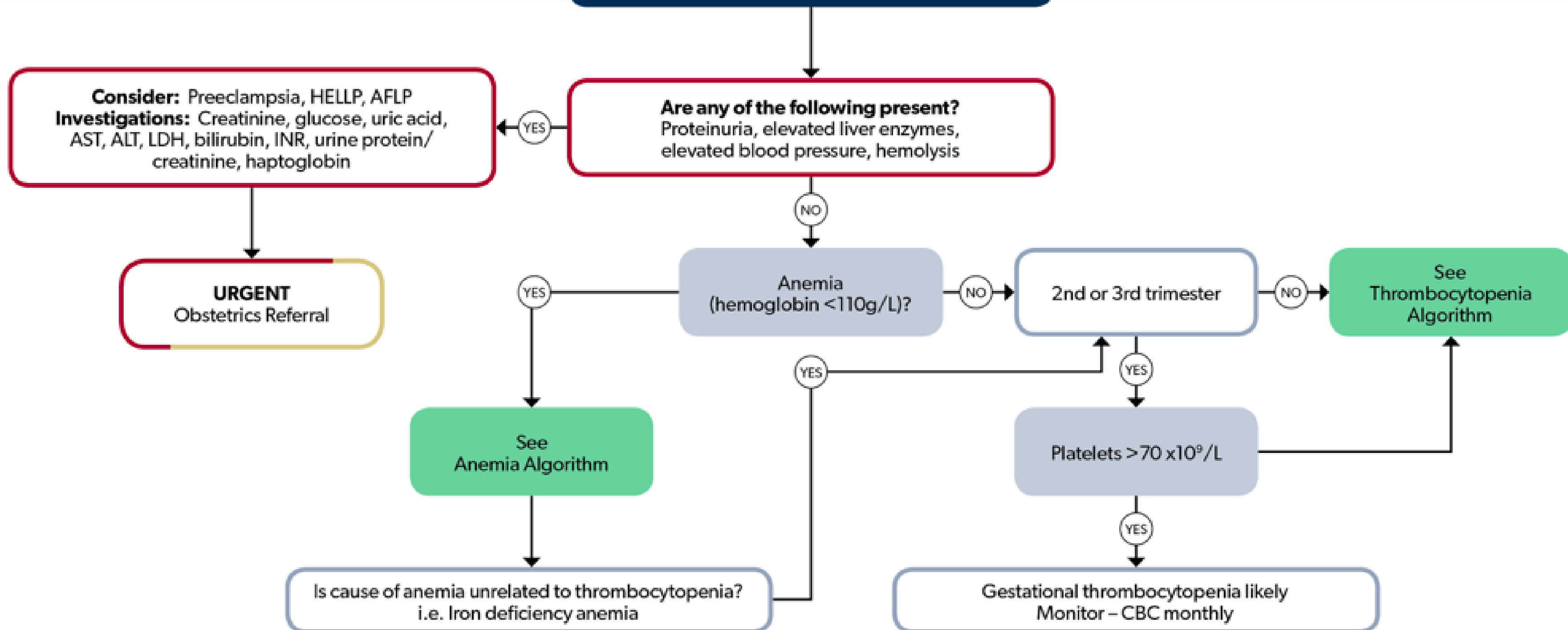


Thrombocytopenia in Pregnancy
(Platelets <130 x10^9/L)
Are any of the following present?
Proteinuria, elevated liver enzymes, elevated blood pressure, hemolysis
YES
Consider: Preeclampsia, HELLP, AFLP
Investigations: Creatinine, glucose, uric acid, AST, ALT, LDH, bilirubin, INR, urine protein/ creatinine, haptoglobin
URGENT
Obstetrics Referral
NO
Anemia
(hemoglobin <110g/L)?
YES
See
Anemia Algorithm
Is cause of anemia unrelated to thrombocytopenia?
i.e. Iron deficiency anemia
YES
NO
2nd or 3rd trimester
NO
See
Thrombocytopenia
Algorithm
YES
Platelets >70 x10^9/L
Gestational thrombocytopenia likely
Monitor – CBC monthly

Case 2

- 32 year old female, G2P1 at 32 weeks
- Diagnosed with preeclampsia at 28 weeks
- Complains of RUQ pain

Test	Value	Ref Range
WBC	12 x 10^9/L	4.5-11.0 x 10^9/L
Hemoglobin	83 g/L	120 – 160 g/L
MCV	88 fL	80– 98 fL
Platelets	45 x 10^9/L	140 – 440 x 10^9/L



Thrombocytopenia in Pregnancy
(Platelets <130 x10⁹/L)
Are any of the following present?
Proteinuria, elevated liver enzymes, elevated blood pressure, hemolysis
YES
Consider: Preeclampsia, HELLP, AFLP
Investigations: Creatinine, glucose, uric acid, AST, ALT, LDH, bilirubin, INR, urine protein/ creatinine, haptoglobin
URGENT
Obstetrics Referral
NO
Anemia (hemoglobin <110g/L)?
YES
See Anemia Algorithm
Is cause of anemia unrelated to thrombocytopenia? i.e. Iron deficiency anemia
YES
NO
2nd or 3rd trimester
NO
See Thrombocytopenia Algorithm
YES
Platelets >70 x10⁹/L
YES
Gestational thrombocytopenia likely
Monitor – CBC monthly

Case 2

Test	Value	Ref. Range
Blood Pressure	145/95	<140/90
Creatinine	83 µmol/L	50 – 90 µmol/L
LDH	800 U/L	90 – 230 U/L
Total Bilirubin	45 µmol/L	<26 µmol/L
Haptoglobin	<0.1 g/L	0.3 – 2.0 g/L
ALT	95 U/L	5 – 32 U/L
Urinalysis	Protein 3+	Negative

Thrombocytopenia in Pregnancy
(Platelets <130×10^9/L)

Are any of the following present?
Proteinuria, elevated liver enzymes, elevated blood pressure, hemolysis

YES →

Consider: Preeclampsia, HELLP, AFLP
Investigations: Creatinine, glucose, uric acid, AST, ALT, LDH, bilirubin, INR, urine protein/creatinine, haptoglobin

URGENT
Obstetrics Referral

NO →

Anemia
(hemoglobin <110g/L)?

YES → See Anemia Algorithm → Is cause of anemia unrelated to thrombocytopenia? i.e. Iron deficiency anemia → YES → 2nd or 3rd trimester

NO → 2nd or 3rd trimester

2nd or 3rd trimester: NO → See Thrombocytopenia Algorithm

2nd or 3rd trimester: YES → Platelets >70×10^9/L

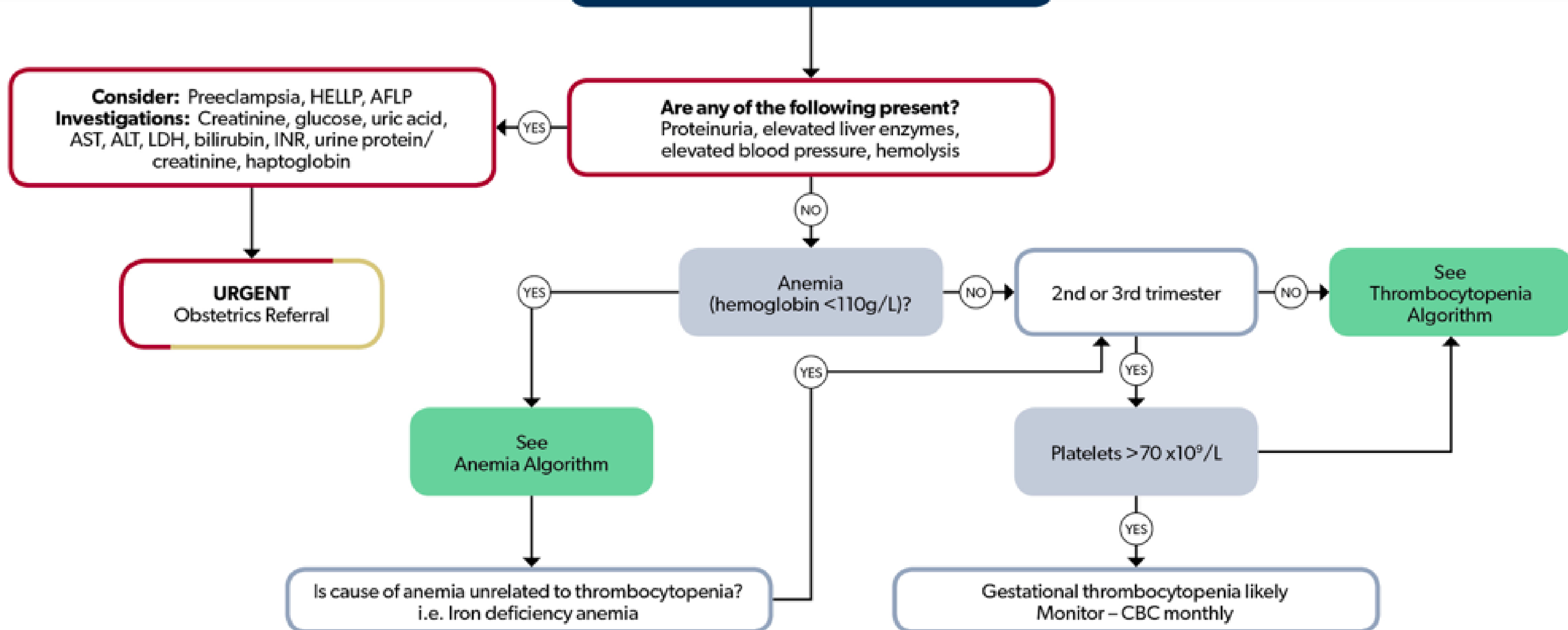
Platelets >70×10^9/L → See Thrombocytopenia Algorithm

Platelets >70×10^9/L: YES → Gestational thrombocytopenia likely
Monitor – CBC monthly

Case 3

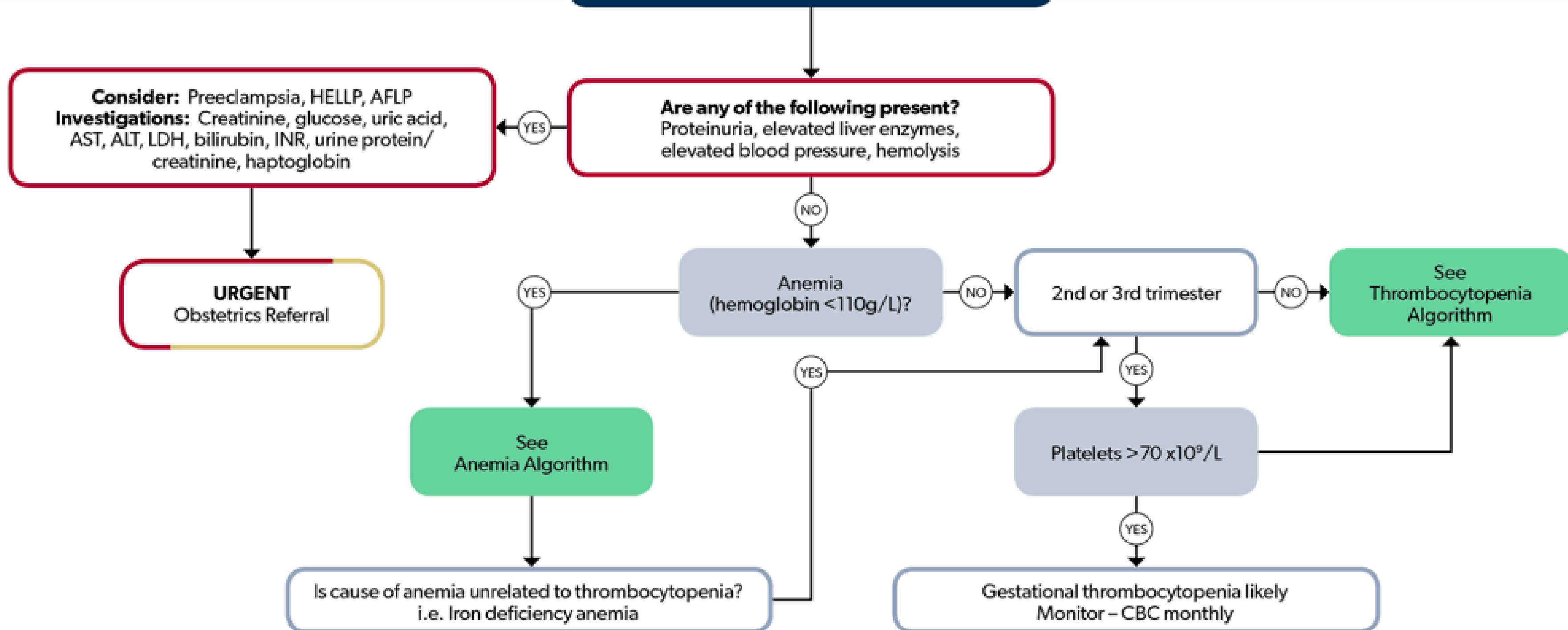
- 32 year old female, G2P1 at 8 weeks
- Routine bloodwork:

Test	Value	Ref Range
WBC	10.6 x 10^9/L	4.5-11.0 x 10^9/L
Hemoglobin	123 g/L	120 – 160 g/L
MCV	88 fL	80– 98 fL
Platelets	62 x 10^9/L	140 – 440 x 10^9/L


Thrombocytopenia in Pregnancy
(Platelets <130 x10⁹/L)
Are any of the following present?
Proteinuria, elevated liver enzymes, elevated blood pressure, hemolysis
YES
Consider: Preeclampsia, HELLP, AFLP
Investigations: Creatinine, glucose, uric acid, AST, ALT, LDH, bilirubin, INR, urine protein/ creatinine, haptoglobin
URGENT
Obstetrics Referral
NO
Anemia
(hemoglobin <110g/L)?
YES
See
Anemia Algorithm
Is cause of anemia unrelated to thrombocytopenia?
i.e. Iron deficiency anemia
YES
NO
2nd or 3rd trimester
NO
See
Thrombocytopenia
Algorithm
YES
Platelets >70 x10⁹/L
YES
Gestational thrombocytopenia likely
Monitor – CBC monthly

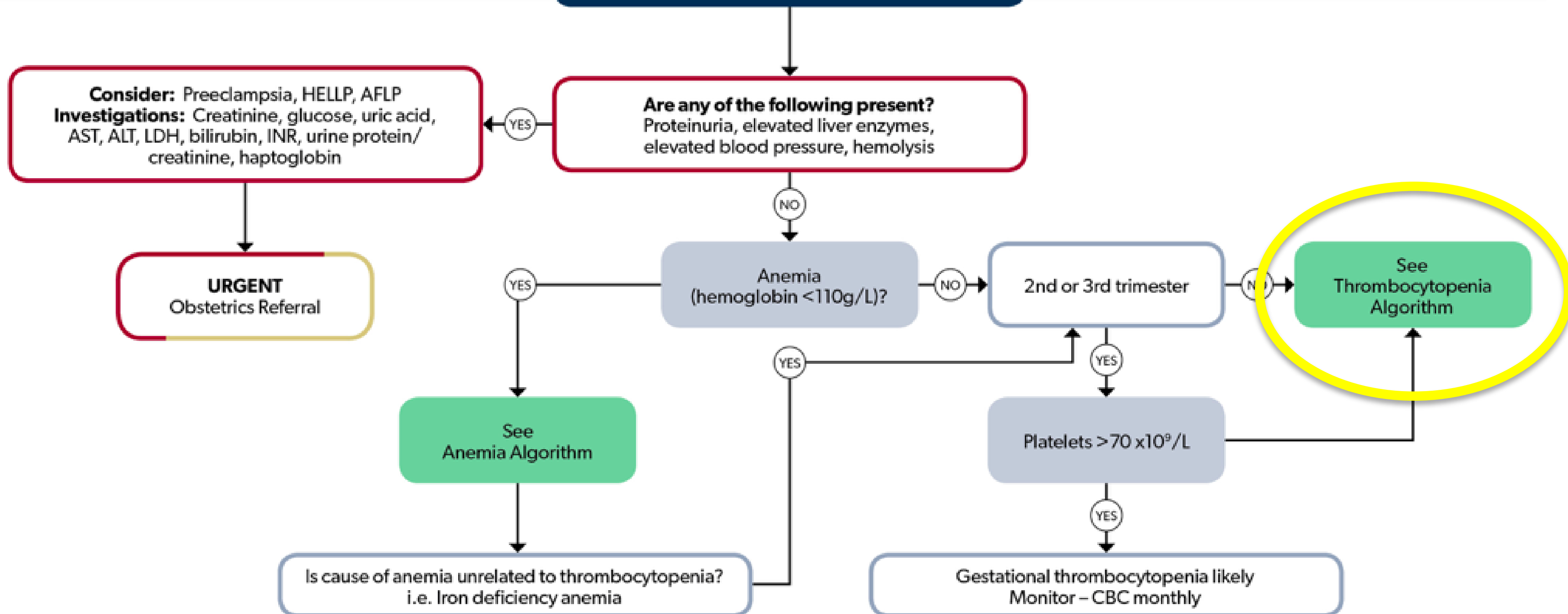
Case 3

Test	Value	Ref. Range
Blood Pressure	105/67	<140/90
Creatinine	51 µmol/L	50 – 90 µmol/L
LDH	140 U/L	90 – 230 U/L
Total Bilirubin	15 µmol/L	<26 µmol/L
Haptoglobin	2.1 g/L	0.3 – 2.0 g/L
ALT	18 U/L	5 – 32 U/L
Urinalysis	Protein negative	Negative

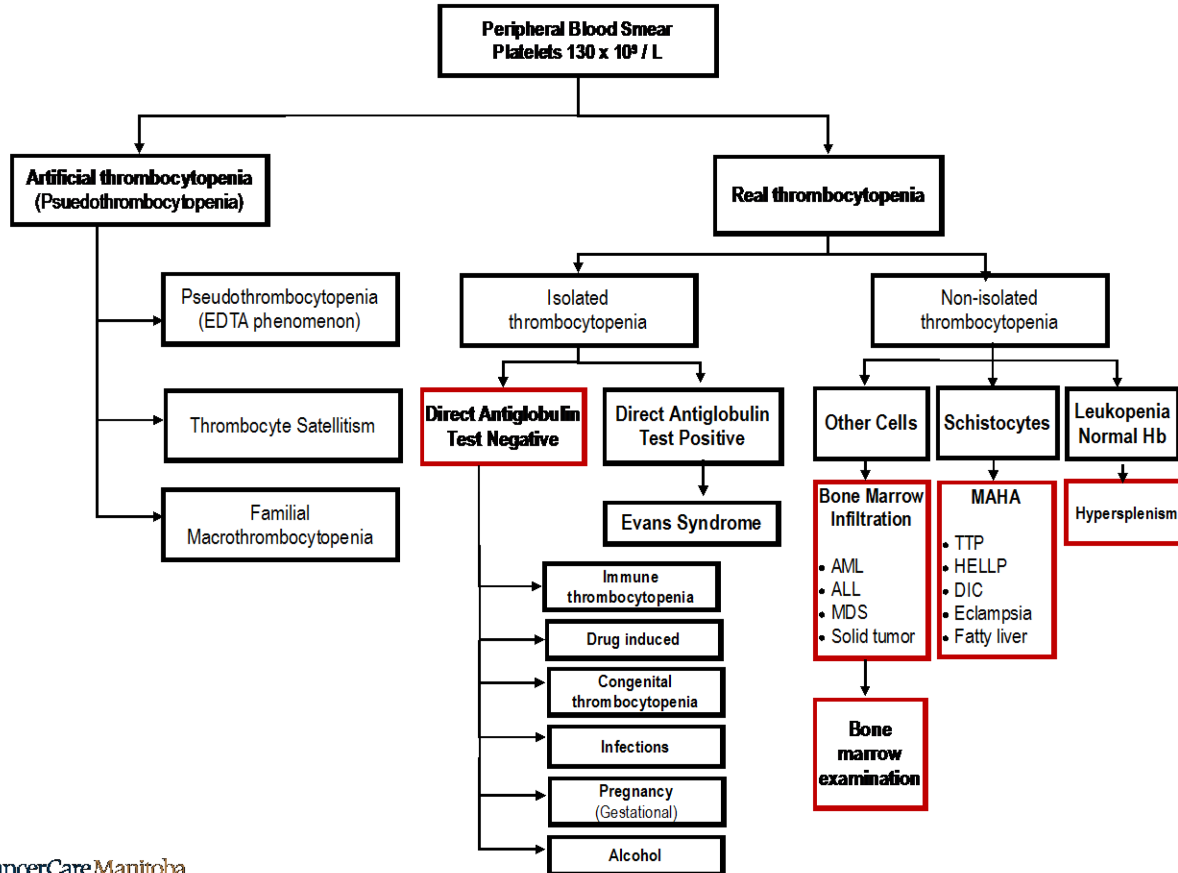

Thrombocytopenia in Pregnancy
(Platelets <130 x10⁹/L)
Are any of the following present?
Proteinuria, elevated liver enzymes, elevated blood pressure, hemolysis
YES
Consider: Preeclampsia, HELLP, AFLP
Investigations: Creatinine, glucose, uric acid, AST, ALT, LDH, bilirubin, INR, urine protein/ creatinine, haptoglobin
URGENT
Obstetrics Referral
NO
Anemia
(hemoglobin <110g/L)?
YES
See
Anemia Algorithm
Is cause of anemia unrelated to thrombocytopenia?
i.e. Iron deficiency anemia
YES
NO
2nd or 3rd trimester
NO
See
Thrombocytopenia
Algorithm
YES
Platelets >70 x10⁹/L
YES
Gestational thrombocytopenia likely
Monitor – CBC monthly

Case 3

Test	Value	Ref Range
WBC	10.6 x 10^9/L	4.5-11.0 x 10^9/L
Hemoglobin	123 g/L	120 – 160 g/L
MCV	88 fL	80– 98 fL
Platelets	62 x 10^9/L	140 – 440 x 10^9/L


Thrombocytopenia in Pregnancy
(Platelets <130 x10⁹/L)
Are any of the following present?
Proteinuria, elevated liver enzymes, elevated blood pressure, hemolysis
YES
Consider: Preeclampsia, HELLP, AFLP
Investigations: Creatinine, glucose, uric acid, AST, ALT, LDH, bilirubin, INR, urine protein/creatinine, haptoglobin
URGENT
Obstetrics Referral
NO
Anemia
(hemoglobin <110g/L)?
YES
See
Anemia Algorithm
Is cause of anemia unrelated to thrombocytopenia?
i.e. Iron deficiency anemia
YES
NO
2nd or 3rd trimester
See
Thrombocytopenia
Algorithm
YES
Platelets >70 x10⁹/L
YES
Gestational thrombocytopenia likely
Monitor – CBC monthly

Work-Up of THROMBOCYTOPENIA



Modified from Erkurt, Kaya, Berber, Koroglu, Kuku (2012) ©Hematology DSG FINAL (Moltzan)

Pathways are subject to clinical judgment and actual practice patterns may not always follow the proposed steps in this pathway.

Take home messages

- Gestational thrombocytopenia is the most common cause of thrombocytopenia in pregnancy
- Rule out hemolysis, and look for systemic concerns (BP, liver enzymes, urinalysis)
- Thrombocytopenia that occurs in the first trimester, or is severe ($<70 \times 10^9$/L), requires investigation
- Iron deficiency anemia is common in pregnancy

CancerCare Manitoba
ActionCancerManitoba

Thank you

cmenard@cancercare.mb.ca

aponnampalam@cancercare.mb.ca

UNIVERSITY OF MANITOBA

CancerCare Manitoba
COMMUNITY ONCOLOGY PROGRAM