Reviewed By
RAAOUM M. JABOR

Anemia in Pregnancy

Objectives:

- → Define anemia in pregnancy.
- → Identify the common types of anemia in pregnancy diagnosed in Saudi Arabia
- → Identify the causes and complications of iron-deficiency anemia in pregnancy.
- → Describe the clinical picture of anemia in pregnancy.

- → Slides
- → Important
- → Golden notes
- → Extra
- → Doctor's notes
- → Previous Doctor's notes
- → Reference

Kaplan Video

Editing File

Anemia in Pregnancy

Epidemiology:

→ Global health problem, common in KSA due to poor diet quality.
→ Commonest medical disorder in pregnancy.
→ Prevalence varies from population to another.
  → **Prevalence in India:** 50 - 70%.
  → **Prevalence in USA:** 2 - 4%.
→ **Commonest type:** nutritional anemia (iron deficiency) because baby = ↑ demand.
→ An important contributor to maternal & perinatal morbidity & mortality as a direct or indirect cause +
→ ↑ bleeding risk.
→ Ferritin is an indicator for iron reserve.
→ **Prevalence:** 30% of reproductive-age females.
→ **Prevalence in pregnancy (***from WHO***):** > 40% of pregnancies (higher among pregnant females).
→ **Prevalence in black pregnant females:** 2x ↑ than non-Hispanic White females.
→ **Major cause of anemia in reproductive-age women:** low or absent iron stores → most common anemia is iron deficiency anemia.

Definition / Thresholds:

→ **Anemia:** a condition where circulating levels of Hb are quantitatively or qualitatively lower than normal.
→ Anemia is defined differently during pregnancy compared with nonpregnant females.
  → **Hemoglobin concentration in pregnancy or puerperium:** <10 g/dL.
  → **Hemoglobin concentration in nonpregnant woman:** 12 g/dL is the lower normal limit.
→ Lower normal limit of **hemoglobin concentration** may vary in different populations.
→ It is helpful to have a threshold for determining the presence and severity of anemia.
→ **Postpartum:** iron parameters may be more meaningful than hemoglobin concentration.
→ **Anemia in pregnancy can be definition (***based mostly on data in nonpregnant individuals***):**

	Non pregnant	Pregnant		Postpartum
		1st and 3rd trimester	2nd trimester	
Hemoglobin	12-15 g/dL	< 11 g/dL[1]	< 10.5 g/dL	<10 g/dL
Hematocrit[2]		< 33%	<32%	<30%

→ **Severity Classification:** *mentioned by the doctor*

	Mild	Moderate	Severe	Very Severe
Hemoglobin	10 - 10.9 gm% 11 - 12	7 or 8 - 9.9 gm%	<7 - 8 gm%	< 4 gm%

1. In pregnancy the cutoff point is 11 (mg/dl) or (%).
2. HCT has no true value, its mere calculations.

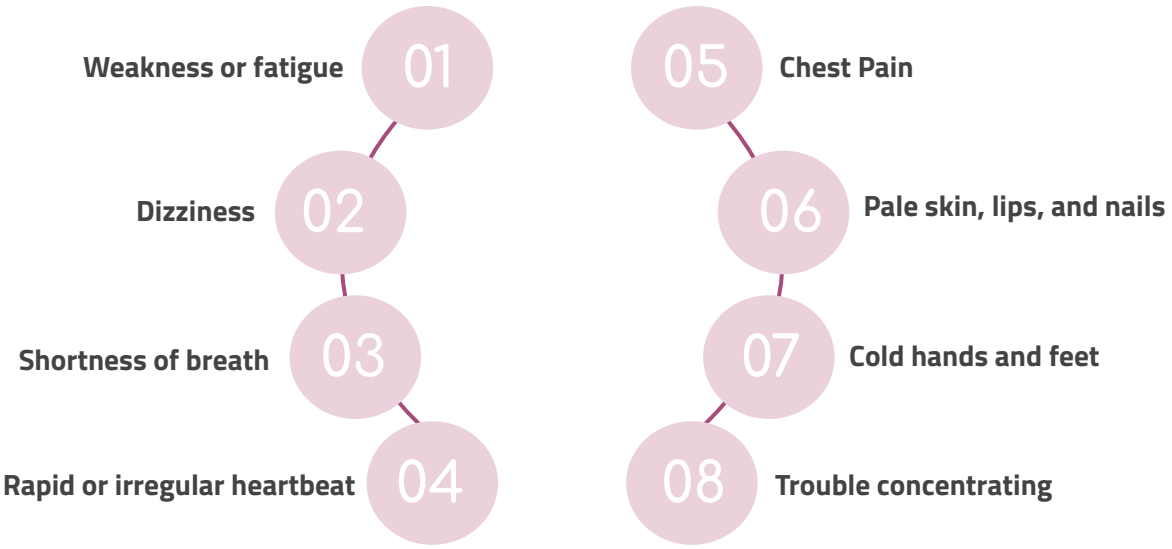
Anemia in Pregnancy

Thresholds & Baseline:

→ Sometimes there is significant ↓ from baseline, without crossing the threshold → clinical judgment to determine reason + need for further evaluation:
- → **Baseline hemoglobin:** 14 g/dL | **Current hemoglobin:** 11 g/dL (↓↓) + macrocytosis → reticulocyte count + vitamin B12 test + folate deficiencies test.
- → **Baseline hemoglobin:** 14 g/dL | **Current hemoglobin:** 11 g/dL (↓↓) + no macrocytosis → iron deficiency test + vitamin B12 test + folate deficiencies test.

Symptoms:

→ Please note that the following symptoms are usually physiological occurring in pregnancy, so keep that in mind but do look at the whole picture.



Effects:

Pregnancy & Mother[1]

→ Predisposed to infections: UTI & puerperal sepsis.
→ Increased risk to postpartum hemorrhage.
→ Subinvolution of uterus.
→ Lactation failure.
→ Maternal mortality, due to:
- → CHF
- → Cerebral anoxia
- → Sepsis
- → Thromboembolism

Fetus & Neonates[2]

→ Higher incidence of abortions, preterm birth, intrauterine growth restriction (IUGR).
→ Intrauterine fetal death (IUFD).
→ Low APGAR at birth.
→ Neonate more susceptible for anemia & infections.
→ Higher Perinatal morbidity & mortality.
→ Anemic infant with cognitive & affective dysfunction.

1. **4 for mother:** Bleeding, Infection (heme build up in urine), Involution of uterus → lactation issues, Maternal mortality.
2. **4 for baby:** Abortion, Preterm labor, IUGR, Fetal mortality and morbidity.

Anemia in Pregnancy

Causes:

→ **Most common causes of anemia during pregnancy (***low hemoglobin concentrations during pregnancy***):**
1. **Physiologic anemia of pregnancy:** not a pathologic condition.
2. **Iron deficiency:** very common in reproductive-age females, even if never pregnant.

→ Other potential causes of anemia should not be overlooked.

1 Physiologic (Dilutional)

→ Pregnancy → physiologic changes → dilutional anemia + overall ↑ RBC mass (to a lesser extent ≈*15 - 25%*).
→ **Plasma volume:**
  → **6 - 12 weeks of gestation:** ↑ by 10 - 15%.
  → **Until 30 - 34 weeks of gestation:** expands rapidly.
  → **Until term:** plateaus or ↓ slightly.
→ **Total gain at term:** 1100 - 1600 mL → **total plasma volume:** 4700 – 5200 mL (*40 - 50% > pre pregnancy*).
→ Pregnancy changes → mild anemia (**hemoglobin:** 10 - 11 g/dL).
→ No specific hemoglobin value can distinguish physiological dilutional anemia & other anemia causes.

2 Iron Deficiency

→ **Physiologic iron loss:** ≈1 mg/day in adults | Childbearing age females require additional daily iron to compensate for menstruation.
→ Expanding mother blood volume + fetal iron requirements for RBC production & fetoplacental growth → dramatically ↑ iron requirements in pregnancy.
  → **Cumulative total requirements for expansion of the maternal RBC mass:** ≈ 500 mg.
  → **Cumulative total requirements for fetal RBC production/fetoplacental growth:** ≈ 300 - 350 mg.
→ **Causes of iron deficiency:**
  → Some parts of world (**resource-limited** settings) → insufficient dietary iron.
  → **Blood losses:** previous pregnancy and/or menstruation → iron deficiency or borderline iron stores.
  → **Short inter-partum interval** → iron deficiency or borderline iron stores.
→ **Iron requirements in pregnancy:**
  → **1st trimester:** ≈ 1 - 2 mg/day (*due to normal gastrointestinal sloughing and early pregnancy-related ↑ RBC mass, similar to normal requirements in non-gravid state*).
  → **2nd trimester:** 4 - 5 mg/day (*due to ↑ maternal & fetal RBC production + fetoplacental growth*).
  → **3rd trimester:** ≈ 6 mg/day (*due to ongoing maternal & fetal RBC production + fetoplacental growth*).

3 Folate Deficiency

→ **Folate deficiency:** most common cause of **megaloblastic** anemia during pregnancy.
→ **Often associated with diets low in:** animal proteins - fresh leafy vegetables -legumes.
→ **Recommended daily folate intake:** 400 - 800 mcg (*1 month prior to attempting conception → throughout pregnancy*).
→ Dose consistent with general population recommendation → 🚫maternal folate deficiency & neural tube defects.
→ Documented folate deficiency → supplemental folic acid (1 mg/day) advised prior to conception.
  → More than sufficient to prevent folate deficiency & fetal neural tube defects associated with folate deficiency.

Anemia in Pregnancy

Causes:

4

Vitamin B12 Deficiency

→ A cause of **macrocytic** anemia in pregnancy.
→ **Causes:**
  → Partial or total gastrectomies.
  → Crohn disease.
  → Bariatric surgery (Roux-en-Y gastric bypass in 75%) patients (almost 50%).
  → Autoimmune hemolysis in SLE - acute viral infection.
  → Hypothyroidism.
  → Chronic kidney disease.

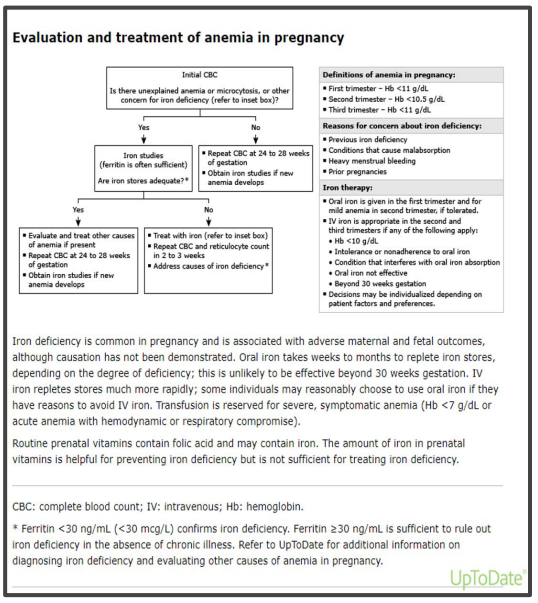
5

Other Causes

→ Much less common in pregnancy.
→ Some inherited and acquired causes of anemia.
→ **Causes:**
  → Hemoglobinopathies
  → Thalassemia
  → Sickle cell
  → RBC membrane disorders
  → Acquired anemias

Screening During Pregnancy:

→ **Screen:** all pregnant women for anemia at **first prenatal visit** complete blood count (CBC) + appropriate prenatal testing.
→ **Repeat screening:** CBC at weeks 24 to 28.
→ Evaluated & treated according to standard guidelines.
→ **Whether to screen for iron deficiency:** anemia patients should be evaluated for the cause (***most common:*** *iron deficiency*).
→ **How to screen for iron deficiency:**
  → Ferritin level is generally sufficient for screening for iron deficiency.
  → Some individuals with iron deficiency may have normal serum ferritin → require transferrin saturation (TSAT) to diagnose iron deficiency.



Good for you to read

Anemia in Pregnancy

Complication:

1

Anemia Complication During Pregnancy:

→ Placental abruption
→ Preterm birth
→ Severe postpartum hemorrhage
→ Maternal shock
→ Maternal intensive care unit (ICU) admission
→ **2x ↑ severe maternal morbidity (SMM):** maternal death - eclampsia - transfusion - hysterectomy - ICU.
→ Antenatal/postnatal maternal sepsis.
→ Cesarean delivery.
→ Future maternal cardiovascular disease

2

Anemia Effects on Fetus

→ **If maternal anemia is identified in the first 30 weeks of pregnancy (***compared to after 30 weeks or no maternal anemia***):**
  → ↑ risks of autism spectrum disorder.
  → ↑ risks of attention deficit hyperactivity disorder.
  → ↑ risks of intellectual disability.
→ ↑ rates of fetal distress.
→ ↑ rates of admission to neonatal intensive care unit.
→ **Low birth weight:** small for gestational age birth weight.

Pathophysiology:

Blood Volume

→ ↑ **blood volume (plasma)** by 40-45% in pregnancy (between 10 - 24 weeks).
→ ↑ plasma > ↑ red cell mass → hemodilution + ↓ hemoglobin level (*plasma levels > RBC mass*).

Red Cell Mass

→ ↑ **RBC mass** (due to ↑ maternal erythropoietin production).

Hematocrit

→ ↓ **hematocrit:**
  → **healthy non-pregnant women:** 38 - 45%.
  → **Late single pregnancy:** ≈ 34%.
  → **late multifetal pregnancy:** 30%.

Iron Stores

→ ↓ with each pregnancy.
→ Too soon & too many pregnancies → ↑ iron deficiency anemia prevalence.
→ Iron / hematinic supplements → ↑ RBC mass *in a more proportionate manner* → ↓ pronounced changes in hemoglobin

Anemia in Pregnancy

Evaluation:

Iron Deficiency Anemia:

→ **Gravida with anemia** → should have prompt testing for iron deficiency (*because it's the most common non physiologic anemia in pregnancy*).
→ Microcytosis may be present.
→ Microcytosis is a late finding.
→ Gravidas without comorbidities → test serum ferritin level alone.
→ **Low:** < 30 ng/mL or < 30 mcg/L → confirm iron deficiency diagnosis.
→ **High:** ≥30 ng/mL → eliminate iron deficiency possibility.

Other Types of Anemia:

→ Anemia features suggest another condition or negative iron deficiency (adequate iron stores) → test other causes of anemia.
  → **Thalassemia:** extreme microcytosis (MCV < 8 0 fL).
  → **Vitamin B12 | Folate Deficiency | Reticulocytosis:** macrocytosis (MCV >100 fL) due to hemolysis.
  → **Other cytopenias (such as thrombocytopenia or neutropenia):**
    → Abnormally high white blood cell (WBC) count or platelet count.
    → Abnormal RBC or WBC morphologies.
    → Failure of anemia to correct with iron supplementation.

Laboratory Findings in Iron Deficiency Anemia Stages:

	Normal	Iron deficiency without anemia	Iron deficiency with mild anemia	Iron deficiency with severe anemia
Hemoglobin	Normal range*	Normal range*	**9 to 12 g/dL (90 to 120 g/L)**	**6 to 7 g/dL (60 to 70 g/L)**
Red blood cell size and appearance	Normal	Normal	**Normal or slight hypochromia (slight decrease in MCHC)**	**Microcytosis (decrease in MCV) and hypochromia (decrease in MCHC)**
Serum ferritin	40 to 200 ng/mL (40 to 200 mcg/L; 89.9 to 449 picoM/L)	**<40 ng/mL¶ (<40 mcg/L; <89.9 picoM/L)**	**<20 ng/mL (<20 mcg/L; <45 picoM/L)**	**<10 ng/mL (<10 mcg/L; <22.5 picoM/L)**
Serum iron	60 to 150 mcg/dL (10.7 to 26.7 microM/L)	60 to 150 mcg/dL (10.7 to 26.7 microM/L)	**<60 mcg/dL (<10.7 microM/L)**	**<40 mcg/dL (<7.1 microM/L)**
Total iron-binding capacity (TIBC; transferrin)	300 to 360 mcg/dL (53.7 to 64.4 microM/L)	300 to 390 mcg/dL (53.7 to 69.8 microM/L)	**350 to 400 mcg/dL (62.6 to 71.6 microM/L)**	**>410 mcg/dL (>73.4 microM/L)**
Transferrin saturation (serum iron/TIBC)	20 to 50%	20%	**<15%**	**<10%**
Reticulocyte hemoglobin[1]	30.6 to 35.4 pg	22.3 to 34.7 pg	14.8 to 34.0 pg	Data not available
Bone marrow iron stain	Adequate iron present	**Iron absent**	**Iron absent**	**Iron absent**
Erythrocyte zinc protoporphyrin, ng/mL RBC	30 to 70	30 to 70	**100 to 200**	**100 to 200**

Bold type illustrates the progression of changes and the tests most likely to define the various stages of iron deficiency. Decreased serum ferritin and absent bone marrow iron are the earliest changes, followed by decreases in TSAT.

- Serum iron may be low in anemia of chronic disease or increased by a recent meal or normal diurnal variation and by itself cannot be used to diagnose iron deficiency.
- Serum ferritin may be increased by other conditions such as acute inflammation, liver disease, and idiopathic pulmonary hemosiderosis.
- TSAT is a calculated ratio (TSAT = iron ÷ TIBC × 100); using a fasting sample (or avoiding iron supplements or an iron-rich meal) may be helpful if there is concern that oral iron intake has affected the serum iron level.
- Bone marrow iron stain (the gold standard) and erythrocyte zinc protoporphyrin (a nonspecific finding) are not routinely used in the evaluation or diagnosis of iron deficiency.

Refer to UpToDate for our approach to diagnostic testing.

MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; TIBC: total iron binding capacity; RBC: red blood cell; TSAT: transferrin saturation.

* The normal range for hemoglobin varies by age and sex (adult men, 14 to 17.5 g/dL; adult women, 12.3 to 15.3 g/dL; children, refer to UpToDate topic on anemia in children).

¶ The exact value is not well established; some clinicians may use a lower value for diagnosing iron deficiency.

Anemia in Pregnancy

Most Critical Period:

→ 28 - 30 weeks of pregnancy (3rd trimester).
→ Labor.
→ Immediately after delivery.
→ Early puerperium.
→ CHF (*failure to cope up with pregnancy induced cardiac load*).

Investigations:

→ **Severity of anemia:**
  → **Hemoglobin & haematocrit:** first visit - 28 to 30 weeks - 36 weeks.
  → Hb electrophoresis.
→ **Type of anemia:**
  → GBP microcytic - macrocytic - dimorphic - normocytic - hemolytic - pancytopenia.
→ **Bone marrow activity:**
  → Reticulocyte count (**normal:** 0.2 - 2%).
  → ↑ **bone marrow activity is seen in:**
    → Hemolytic anemia
    → Following acute blood loss
    → Iron def anemia on treatment
→ **Cause of anemia:**
  → Various investigations.

Special Investigations:

→ **Serum Ferritin → iron reserve indicator:**
  → Abnormal if <20 ng/ml (**normal:** 40 - 160 ng/dl).
  → Assess iron stores.

→ **Serum Iron:**
  → **Normal:** 65 - 165 ug/dl.
  → ↓ serum iron → iron deficiency anemia.

→ **Serum Iron binding capacity:**
  → **Normal:** 300 - 360 ug/dl.
  → ↑ with anemia severity.

→ **Percentage saturation of transferrin:**
  → **Normal:** 35 - 50%.
  → ↓ to less than 20% → iron deficiency anemia.

→ **RBC Protoporphyrin**
  → **Normal:** 30 ug/dl.
  → Doubles or triples → iron deficiency anemia (*substrate to bind with Fe, can not be converted into Hb in Fe deficiency*).

→ **Vitamin B12**

Anemia in Pregnancy

Management:

Prevention of iron deficiency

→ **"Low dose" supplementation:** oral iron 27 - 30 mg daily throughout pregnancy to all pregnant individuals → compensate for ↑ iron demands + corresponds to amount of iron in most iron-containing prenatal vitamins.
→ Intolerant of iron in prenatal vitamins → prenatal vitamins without iron + supplement with oral iron supplements on an every-other-day basis.

Treatment of Iron Deficiency

→ **Uncomplicated iron deficiency (regardless of hemoglobin level):** give iron doses higher than prenatal vitamins.
  → Antenatal maternal iron treatment → ↑ hemoglobin level in ≈ 2 weeks (*the time it takes to create new RBCs in the bone marrow*).
  → Gravidas + severe anemia + 2-week delay expected to result in significant morbidity → transfusion and/or referral to a specialist (hematologist).
→ **Factors affecting the choice between oral and intravenous (IV) iron:** *both effective for replenishing iron stores.*

Advantages and disadvantages of oral versus IV iron

	Advantages	Disadvantages
Oral iron	• Effective for most patients • Extremely low risk of serious adverse events • Initial costs very low	• Gastrointestinal side effects are common • Compliance may be low • May be inadequate for severe or ongoing blood loss • May require administration for several months • Total costs may be higher
IV iron	• Effective for most patients • More rapid correction of anemia and resolution of symptoms • Ability to administer large doses (up to 1000 mg elemental iron) in a single infusion • Compliance is assured • No gastrointestinal side effects	• Requires monitored intravenous infusion • Rare cases of allergic or infusion reactions • Requires equipment and personnel to treat allergic or infusion reactions • Initial costs may be higher

  → **Oral:**
    → **Given to:**
      → Most gravidas that can tolerate it (*it's ADRs*).
      → Gravidas treated during 1st trimester.
    → Safe.
    → Inexpensive.
    → Readily available.
    → Often adequate therapy.
    → **Ferrous sulfate (FS):** most commonly prescribed oral formulation.
      → Up to 70% of those to whom it is prescribed report significant GI perturbation.
    → **Dosing:** 40 - 200 mg elemental iron per day.
    → **ADRs:**
      → **GI side effects:** metallic taste - gastric irritation - nausea - diarrhea - constipation.
        → Constipation is exacerbated by enlarging gravid uterus pressing posteriorly on rectum + ↑ progesterone levels → slow bowel transit.
    → **To improve tolerability:**
      → Extending interval between doses.
      → Switching to a liquid that can be more easily titrated.
      → Switching to intravenous iron (if in second or third trimester).
    → **Mostly ineffective in IBD patients due to:**
      → Worsening GI symptoms - ↓ absorption - effect on bowel flora.
    → **Bariatric surgery patients (*Roux-en-Y bypass or biliopancreatic procedures*):**
      → Oral iron can't be exposed to stomach gastric acid (required to protect it from alkaline pancreatic secretions) → iron is converted to ferric hydroxide (rust) → iron not absorbed.
  → **IV:**
    → Gravidas treated beyond 1st trimester.
    → Gravidas that can't tolerate oral iron.
    → Gravidas who have severe anemia especially later in pregnancy.
    → Gravidas whom oral iron does not effectively ↑ hemoglobin and/or ferritin levels.
    → IBD & bariatric surgery patients.

Assessing response to treatment

→ **Expected response to iron repletion:**
  → Improvement in RBC production (begins with reticulocytosis after ≈ 1 week).
  → ↑ hemoglobin level of at least 1 g/dL within 2 - 3 weeks.
  → ↑ serum ferritin into normal range within 3 weeks.

Anemia in Pregnancy

Iron Deficiency Anemia:

OB Triad

Iron Deficiency Anemia

- → **Hemoglobin:** <10 g
- → **MCV:** < 80 mm^3
- → **RDW:** >15%

Definition:

- → Nutritional anemia resulting in decreased heme production.
- → The most common anemia in women (*due to menstruation & pregnancy*).

Investigations:

- → CBC & MCV value.
  - → **MCV:** < 80 (↓).
  - → **RBCs:** microcytic and hypochromic.
  - → **Hemoglobin:** <10 g/dL.
  - → **RDW:** >15.
- → Serum iron - ferritin - transferrin.
  - → ↓ serum iron & ferritin + ↑ serum transferrin → confirmed iron deficiency anemia.

Pathophysiology:

- → ↓ hemoglobin values do not occur until complete depletion of iron stores in liver, spleen, and bone marrow → ↓ serum iron + ↑ total iron binding capacity (TIBC).

Pregnancy Requirements:

- → 800 mg of elemental iron:
  - → 500mg goes to expand RBC mass.
  - → 300 mg goes to fetal-placental unit.

Symptoms:

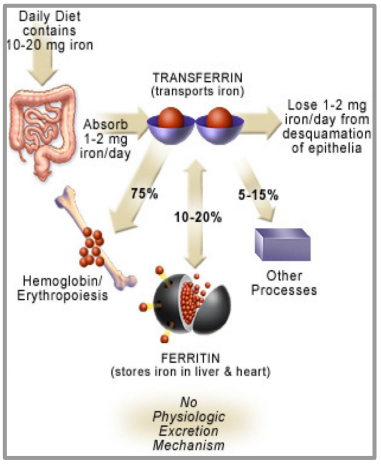
- → **Findings may vary from none to general:**
  - → Malaise.
  - → Palpitations,.
  - → Ankle edema.
- → **Fetal Effects:**
  - → ↑ IUGR.
  - → Preterm birth.

Prevention:

- → Elemental iron 30 mg per day.

Iron Pharmacokinetics & Daily Requirements:

- → **Normal diet:** 14 mg of iron.
- → **Absorption of iron:** 5 - 10% (1 - 2 mg) & 3 - 4% in pure vegetarian diet.
- → **Additional daily iron demand in pregnancy:**
  - → **Early pregnancy:** 2 - 3 mg/day.
  - → **Late pregnancy:** 6 - 7 mg/day.
- → **required daily supplement for pregnant woman:** 40 - 60 mg of elemental iron.
- → **Folic acid requirement for pregnant woman:** ↑ 400 - 600 ug/day → ↓ neural tube defects risk.
- → Strict vegetarian → vitamin B12 is deficient.



Iron Deficiency Anemia:

Treatment:

→ **Ferrous sulfate** 325 mg orally once/day + oral folic acid subelement.
→ **Parenteral therapy:**
  → **IM:** 20% of pregnant women don't absorb enough supplemental oral iron or non-compliance.
  → **IV:** faster ↑ Hb + better replenishment of iron stores in comparison with oral therapy.
→ Improving diet rich in iron such as leafy vegetables.
  → Heme iron (e.g. animal source) is higher and better absorbed.
  → Food fortification with iron.
→ Iron absorption enhanced by citrous fruits and Vitamin C.
→ **Avoid:** Tea - Coffee - Ca - Phytates - Phosphates - Oxalates.
→ Treat worm infections.
→ Iron & folic acid supplementation during pregnancy.

Differentiation between Iron Deficiency Anemia & Thalassemia:

Investigation	Normal Values	Iron Deficiency Anemia	Thalassemia
MCV	75 - 96 fl	Reduced	V reduced
MCH	27 - 33 pg	Reduced	V reduced
MCHC	32 - 35 gm/dl	Reduced	N or reduced
Hb F	< 2%	Normal	Raised
Hb A_2	2 - 3%	N or Reduced	Raised >3%
Serum Iron	60 - 120 ug/dl	Reduced	Normal
Serum Ferritin	15 - 300 ug/dl	Reduced	Normal
TIBC	300 - 350 gu/dl	Raised	Normal
Bone Iron Store		Reduced	Normal
Free Erythrocyte Protoporphyrin (FEP)	< 35 ug/dl	> 50	Normal

Anemia in Pregnancy

Folate Deficiency Anemia:

OB Triad

Folate Deficiency Anemia

- → **Hemoglobin:** <10 g
- → **MCV:** > 100 mm^3
- → **RDW:** >15%

Definition:

- → Megaloblastic Macrocytic Anemia.
- → Nutritional anemia resulting in decreased hemoglobin production.
- → **Prevalence:** 0.5 - 1.5% of pregnant women.
- → ↑ neural tube defect risk.
- → Supplements are given to prevent: anencephaly - spina bifida - syringomyelocele.

Investigations:

- → Measurement of serum folate.
- → Severe megaloblastic anemia may warrant bone marrow examination → further hospital treatment.
- → **RBCs:** macrocytic + ↓ folate levels.
- → **Hemoglobin:** ≤10 g/dL.
- → **MCV:** >100.
- → **RDW:** >15.
- → **Peripheral smear:** hypersegmented neutrophils.

Pathophysiology:

- → Folate stores in the body are usually enough for 90 days.
- → Falling hemoglobin values do not occur until complete depletion of folate stores.

Risk Factors:

- → Chronic hemolytic anemias (such as sickle cell disease).
- → Anticonvulsant use (phenytoin - phenobarbital).
- → Frequent pregnancies.

Treatment:

- → Folate 1 mg orally daily.

Prevention:

- → **All women:** folate 0.4 mg orally daily.
- → **High risk for NTDs:** folate 4 mg orally daily.

Anemia in Pregnancy

Sickle Cell Anemia:

Definition:
→ Inherited autosomal recessive disease ⟶ normal production of abnormal globin chains.

Investigations:
→ **Screening:** peripheral blood tests that detect presence or absence of hemoglobin S, but don't differentiate between disease and trait.
→ Hemoglobin electrophoresis differentiates between sickle cell (SA) trait or sickle cell (SS) disease.
  → **SA trait:** < 40% hemoglobin S.
  → **SS disease:** > 40% hemoglobin S

Effects on Pregnancy::
→ **SA trait:** ↑ UTIs but pregnancy outcome is not changed.
→ **SS disease:** pregnancy may be complicated by ↑ spontaneous abortions.
→ IUGR – fetal deaths - preterm delivery.

Risk Factors:
→ **Only significant risk factor:** African and Mediterranean descent.

Treatment:
→ Avoid hypoxia.
→ Folate supplements.
→ Monitor fetal growth and well-being.

Prevention:
→ **All women:** folate 0.4 mg orally daily.
→ **High risk for NTDs:** folate 4 mg orally daily.

Indications for Blood Transfusion:

→ Severe anemia (Hb < 7) first seen after 36 weeks of pregnancy.
→ Anemia due to acute blood Loss – APH & PPH.
→ Associated Infection.
→ Patient not responding to oral or parenteral therapy.
→ Anemic & symptomatic pregnant women (dyspneic, with heart failure etc).
→ Irrespective of gestational age.

439 Summary

Anemia

- **Incidence:**
  - Most common medical disorder in pregnancy in KSA due to poor diet quality
  - Generally more common in developing/underdeveloped countries
- **Causes:**
  - Nutritional deficiencies: **iron** (most common), folate, vit B12
  - Hemoglobinopathies: sickle cell disease/trait, thalassemia
- **Definition:**
  - A condition where circulating levels of Hb are lower than normal

	Non - Pregnant	Pregnant	
		1st and 3rd trimester	2nd trimester
Hemoglobin	< 12 gm%	< 11 gm%[1]	< 10.5 gm%
Hematocrit[2]		< 33%	

Severity Classification				
	Mild	Moderate	Severe	Very severe
Hemoglobin	10 - 10.9 gm% 11-12	7 - 9.9 gm%	<7 gm%	< 4 gm%

- **Symptoms** (often overlaps with pregnancy symptoms):
  - Weakness, fatigue, dizziness, trouble in concentration
  - Rapid/irregular heartbeat, SOB, chest pain
  - Pale skin/lips, cold extremities
- **Pathophysiology:**
  - **Blood volume:** In pregnancy, blood volume (plasma) increases 40-45% , which results in a concomitant **hemodilution**. Although red blood cell (RBC) mass increases as well during pregnancy, plasma volume increases more, resulting in a relative anemia
  - **Red cell mass:** RBC mass increase is driven by an increase in maternal erythropoietin production
  - **Hematocrit:** It decreases from 38% - 45% in healthy non-pregnant women to about 34% during late single pregnancy and to 30% during late multifetal pregnancy
  - **Iron stores:** measured by serum ferritin, depleted with each pregnancy. Too soon (non-spaced pregnancy) & too many pregnancies (multiparity) result in higher prevalence of iron deficiency anemia. Iron supplements have less pronounced changes in hemoglobin, as they increase their RBCs in a more proportionate manner than those not taking it.

- **Effects of anemia**
  - On pregnancy/mother:
    - Risk factor for UTIs (due to heme buildup in urine), puerperal sepsis
    - Increased bleeding risk; postpartum hemorrhage
    - **Subinvolution of uterus** (slowing of uterus returning to its pre-pregnancy state)
      - **Oxytocin** is responsible for the involution of the uterus
      - **Endometritis** can cause subinvolution
    - Lactation failure
    - Mortality; due to CHF, cerebral anoxia, sepsis, and thromboembolism
  - On fetus/neonate:
    - Higher incidence of abortions, preterm birth, intrauterine growth restriction (IUGR), intrauterine fetal death (IUFD)
    - Low APGAR at birth
    - Increased risk of neonatal anemia (with cognitive & affective dysfunction)
    - Increased risk of neonatal infections
    - Higher perinatal morbidity & mortality
- **Critical periods:**
  - From 28-30 weeks GA to early puerperium
- **Types of anemia in pregnancy:**

	Overview	Diagnosis	Management
Iron deficiency	• Most common type of anemia • Risk factors: chronic bleeding, poor nutrition, **multiparity**	• Hb<10 g/dL, MCV<80, RDW>15 • ↓Serum iron & ferritin (low levels of iron storage),↑transferrin: confirmatory	Prevention: 30 mg elemental iron PO daily Treatment: Oral or IV iron and folic acid supplementation during pregnancy (iron form: ferrous sulfate) • Oral ferrous sulfate and folic acid supplements per day
			• IM or IV ferrous sulfate: in women who: -do not/can't absorb oral iron (e.g., gastritis) -non compliance !
Folate deficiency	• Increases risk of neural tube defects • Risk factors: chronic hemolytic anemia, anticonvulsants, **frequent pregnancies**	• Hb<10, MCV>100, RDW>15 • Serum folate measurement	• Prevention: -0.4 mg Folate PO daily for all women -4 mg Folate PO daily for those at high risk for **neural tube defects** • Treatment: 1 mg folate PO daily
Sickle cell	• Inherited autosomal recessive • Risk factors: african and mediterranean descent • **SA trait: increased risk of UTI**, unchanged pregnancy outcome • SS disease: possible abortion, IUGR, IUGD, preterm delivery	• SA trait: <40% HbS on Hb electrophoresis • SS disease: >40% HbS	Avoid Hypoxia, take folate supplements, and monitor fetal growth and well-being.

- **Indications for Blood Transfusion:**
  - **Severe anemia (Hb < 7)** first seen after 36 weeks of pregnancy
  - Anemia due to acute blood loss – antepartum and postpartum hemorrhage
  - Associated infection
  - Patient not responding to oral or parenteral therapy
  - Anemic & symptomatic pregnant women (dyspneic, with heart failure etc)

Quiz

Question 1:

→ **Iron deficiency anemia is characterized by the following except:**

A. Decreased serum iron
B. Decreased ferritin
C. Decreased serum transferrin

Question 2:

→ **Provide 4 indications for blood transfusion:**

Reference

Normal Values in Pregnancy

The normal values for several hematologic, biochemical, and physiologic indices during pregnancy differ markedly from those in the nonpregnant range and may also vary according to the duration of pregnancy. These alterations are shown in Table 6-1.

Cardiovascular System

CARDIAC OUTPUT

The hemodynamic changes associated with pregnancy are summarized in Table 6-2. **Retention of sodium and water during pregnancy accounts for a total body water increase of 6 to 8 L,** two-thirds of which is located in the extravascular space. **The total sodium accumulation averages 500 to 900 mEq** by the time of delivery. **The total blood volume increases by about 40% above nonpregnant levels, with wide individual variations.** The plasma volume rises as early as the sixth week of pregnancy, and reaches a plateau by about 32 to 34 weeks' gestation, after which little further change occurs. The increase averages 50% in singleton pregnancies, and approaches 70% with a twin gestation. The red blood cell mass begins to increase at the start of the second trimester, and continues to rise throughout pregnancy. By the time of delivery, it is 20-35% above nonpregnant levels. **The disproportionate increase in plasma volume compared with the red cell volume results in hemodilution with a decreased hematocrit reading, sometimes referred to as physiologic anemia of pregnancy.** If iron stores are adequate, the hematocrit tends to rise from the second to the third trimester.

TABLE 6-1
COMMON LABORATORY VALUES IN PREGNANCY

Test	Normal Range (Nonpregnant)	Change in Pregnancy	Timing
Serum Chemistries			
Albumin	3.5-4.8 g/dL	↓ 1 g/dL	Most by 20 wk, then gradual
Calcium (total)	9-10.3 mg/dL	↓ 10%	Gradual fall
Chloride	95-105 mEq/L	No significant change	Gradual rise
Creatinine (female)	0.6-1.1 mg/dL	↓ 0.3 mg/dL	Most by 20 wk
Fibrinogen	1.5-3.6 g/L	↑ 1-2 g/L	Progressive
Glucose, fasting (plasma)	65-105 mg/dL	↓ 10%	Gradual fall
Potassium (plasma)	3.5-4.5 mEq/L	↓ 0.2-0.3 mEq/L	By 20 wk
Protein (total)	6.5-8.5 g/dL	↓ 1 g/dL	By 20 wk, then stable
Sodium	135-145 mEq/L	↓ 2-4 mEq/L	By 20 wk, then stable
Urea nitrogen	12-30 mg/dL	↓ 50%	1st trimester
Uric acid	3.5-8 mg/dL	↓ 33%	1st trimester, rise at term
Urine Chemistries			
Creatinine	15-25 mg/kg/day (1-1.4 g/day)	No significant change	
Protein	Up to 150 mg/day	Up to 250-300 mg/day	By 20 wk
Creatinine clearance	90-130 mL/min/1.73 m^2	↓ 40-50%	By 16 wk
Serum Enzymatic Activities			
Amylase	23-84 IU/L	↑ 50-100%	
Transaminase Glutamic pyruvic (SGPT) Glutamic oxaloacetic (SGOT)	 5-35 mU/mL 5-40 mU/mL	 No significant change No significant change	
Hematocrit (female)	36-46%	↓ 4-7%	Bottoms at 30-34 wk
Hemoglobin (female)	12-16 g/dL	↓ 1.5-2 g/dL	Bottoms at 30-34 wk
Leukocyte count	4.8-10.8 × 10^3/mm^3	↑ 3.5 × 10^3/mm^3	Gradual
Platelet count	150-400 × 10^3/mm^3	Slight decrease	
Serum Hormone Values			
Cortisol (plasma)	8-21 g/dL	↑ 20 g/dL	
Prolactin (female)	25 ng/mL	↑ 50-400 ng/mL	Gradual, peaks at term
Thyroxine (T_4), total	5-11 g/dL	↑ 5 g/dL	Early sustained
Triiodothyronine (T_3), total	125-245 ng/dL	↑ 50%	Early sustained

Data from Main DM, Main EK: *Obstetrics and gynecology: a pocket reference,* Chicago, 1984, Year Book, p 7.

Cardiac output rises by the tenth week of gestation, reaching about 40% above nonpregnant levels by 20 to 24 weeks, after which there is little change. The rise in cardiac output, which peaks while blood volume is still rising, reflects increases mainly in stroke volume and, to a lesser extent, in heart rate. With twin and triplet pregnancies, the changes in cardiac output are greater than those seen with singleton pregnancies.

The cardiovascular responses to exercise are altered during pregnancy. **For any given level of exercise, oxygen consumption is higher in pregnant than in nonpregnant women.** Similarly, the cardiac output for any level of exercise is increased during pregnancy, and the maximum cardiac output is reached at lower levels of exercise. It is not clear that any of the changes in hemodynamic responses to exercise are detrimental to mother or fetus, but it suggests that maternal cardiac reserves may be lower during pregnancy, and shunting of blood away from the uterus may occur during or after exercise.

TABLE 6-2
CARDIOVASCULAR CHANGES IN PREGNANCY

Parameter	Amount of Change	Timing
Arterial blood pressures Systolic Diastolic Mean	 ↓ 4-6 mm Hg ↓ 8-15 mm Hg ↓ 6-10 mm Hg	 All bottom at 20-24 wk, then rise gradually to prepregnancy values at term
Heart rate	↑ 12-18 beats/min	1st, 2nd, 3rd trimesters
Stroke volume	↑ 10-30%	1st and 2nd trimesters, then stable until term
Cardiac output	↑ 33-45%	Peaks in early 2nd trimester, then stable until term

Data from Main DM, Main EK: *Obstetrics and gynecology: a pocket reference,* Chicago, 1984, Year Book, p 18.

INTRAVASCULAR PRESSURES

Systolic pressure falls only slightly during pregnancy, whereas diastolic pressure decreases more markedly; this reduction begins in the first trimester, reaches its nadir in mid-pregnancy, and returns toward nonpregnant levels by term. These changes reflect the elevated cardiac output and reduced peripheral resistance that characterize pregnancy. Toward the end of pregnancy, vasoconstrictor tone, and with it blood pressure, normally increase. The normal, modest rise of arterial pressure as term approaches should be distinguished from the development of pregnancy-induced hypertension or preeclampsia. **Pregnancy does not alter central venous pressures.**

Blood pressure, as measured with a sphygmomanometer cuff around the brachial artery, varies with posture. In late pregnancy, arterial pressure is higher when the gravid woman is sitting compared with lying supine. When elevations in blood pressure are clinically detected during pregnancy, it is customary to repeat the measurement with the patient lying on her left side. This practice usually introduces a systematic error. In the lateral position, the blood pressure cuff around the brachial artery is raised about 10 cm above the heart. This leads to a hydrostatic fall in measured pressure, yielding a reading about 7 mm Hg lower than if the cuff were at heart level, as occurs during sitting or supine measurements.

MECHANICAL CIRCULATORY EFFECTS OF THE GRAVID UTERUS

As pregnancy progresses, the enlarging uterus displaces and compresses various abdominal structures, including the iliac veins and inferior vena cava (and probably also the aorta), with marked effects. **The supine position accentuates venous compression,** producing a fall in venous return and hence cardiac output. In most gravid women, a compensatory rise in peripheral resistance minimizes the fall in blood pressure. In up to 10% of gravid women, a significant fall occurs in blood pressure accompanied by symptoms of nausea, dizziness, and even syncope. This **supine hypotensive syndrome** is relieved by changing position to the left side (the venous return is greater when the patient turns to the left side as compared with the right side). The expected baroreflexive tachycardia, which normally occurs in response to other maneuvers that reduce cardiac output and blood pressure, does not accompany caval compression. In fact, **bradycardia is often associated with the syndrome.**

The venous compression by the gravid uterus in the supine position elevates pressure in veins that drain the legs and pelvic organs, thereby exacerbating varicose veins in the legs and vulva and causing hemorrhoids. The rise in venous pressure is the major cause of the lower extremity edema that characterizes pregnancy. The hypoalbuminemia associated with pregnancy also shifts the balance of the other major factor in the Starling equation (colloid osmotic pressure) in favor of fluid transfer from the intravascular to the extracellular space. **Because of venous compression, the rate of blood flow in the lower veins is also markedly reduced, causing a predisposition to thrombosis.** The various effects of caval compression are somewhat mitigated by the development of a paravertebral collateral circulation that permits blood from the lower body to bypass the occluded inferior vena cava.

During late pregnancy, the uterus can also partially compress the aorta and its branches. This is thought to account for the observation in some patients of lower pressure in the femoral artery compared with that in the brachial artery. This aortic compression can be accentuated during a uterine contraction, and may be a cause of fetal distress when a patient is in the supine position. This phenomenon has been referred to as the **Poseiro effect.** Clinically, it can be suspected when the femoral pulse is not palpable.

REGIONAL BLOOD FLOW

Blood flow to most regions of the body increases and reaches a plateau relatively early in pregnancy. Notable exceptions occur in the uterus, kidney, breasts, and skin, in each of which blood flow increases with gestational age. **Two of the major increases (those to the kidney and to the skin) serve purposes of elimination: the kidney of waste material and the skin of heat.** Both processes require plasma rather than whole blood, which points to the importance of the disproportionate increase of plasma over red blood cells in the blood volume expansion during pregnancy.

Early in pregnancy, renal blood flow increases to levels approximately 30% above nonpregnant levels and remains unchanged as pregnancy advances. This change accounts for the increased creatinine clearance and lower serum creatinine level. Engorgement of the breasts begins early in gestation, with mammary blood flow increasing two to three times in later pregnancy. The skin blood flow increases slightly during the third trimester, reaching 12% of cardiac output.

There is little information on the distribution of blood flow to other organ systems during pregnancy. **The uterine blood flow increases from about 100 mL/min in the nonpregnant state** (2% of cardiac output) **to approximately 1200 mL/min** (17% of cardiac output) **at term.** Uterine blood flow, and thus gas and nutrient transfer, to the fetus is vulnerable. **When maternal cardiac output falls, blood flow to the brain, kidneys, and heart is supported by a redistribution of cardiac output, which shunts blood away from the uteroplacental circulation.** Similarly, changes in perfusion pressure can lead to decreases in uterine blood flow. Because the uterine vessels are maximally dilated during pregnancy, little autoregulation can occur to improve uterine blood flow.

CONTROL OF CARDIOVASCULAR CHANGES

The precise mechanisms accounting for the cardiovascular changes in pregnancy have not been fully elucidated. The rise in cardiac output and fall in peripheral resistance during pregnancy may be explained in terms of the circulatory response to an arteriovenous shunt, represented by the uteroplacental circulation. The elevations in cardiac output and uterine blood flow follow different time courses in pregnancy, however, with the former reaching its maximum in the second trimester and the latter increasing to term.

A unifying hypothesis suggests that the elevations in circulating steroid hormones in combination with increases in production of aldosterone and vasodilators such as prostaglandins, atrial natriuretic peptide, nitric oxide, and probably others, reduce arterial tone and increase venous capacitance. These changes, along with the development of arteriovenous shunts, appear responsible for the increase in blood volume and the hyperdynamic circulation of pregnancy (high-flow, low-resistance). The same hormonal changes cause relaxation in the cytoskeleton of the maternal heart, which allows the end-diastolic volume (and stroke volume) to increase.

OXYGEN-CARRYING CAPACITY OF BLOOD

Plasma volume expands proportionately more than red blood cell volume, leading to a fall in hematocrit. Optimal pregnancy outcomes are generally achieved with a maternal hematocrit of 33-35%. Hematocrit readings below 27%, or above 39%, are associated with less favorable outcomes. **Despite the relatively low "optimal" hematocrit, the arteriovenous oxygen difference in pregnancy is below nonpregnant levels.** This supports the concept that the hemoglobin concentration in pregnancy is more than sufficient to meet oxygen-carrying requirements.

Pregnancy requires about 1 g of elemental iron: 0.7 g for mother and 0.3 g for the placenta and fetus. A high proportion of women in the reproductive age group enter pregnancy without sufficient stores of iron to meet the increased needs of pregnancy.

Med 441 Team:

Leader:

Sarah Alhamlan

Members:

Jumana Alqahtani - Noyer Alshaibany

Good Luck!

Med 438 Team:

Leaders:

Ateen Almutairi - Lama ALzamil

Members:

Rahaf Alshunaiber - Jude Alkhalifa
Nojoud Alabdullatif

Med 439 Team:

Leader:

Bushra Alotaibi

Members:

Alanoud Salman - Shayma Alghanoum
Ghada Alabdi