PHYSIOLOGICAL CHANGES & MEDICAL DISORDERS IN PREGNANCY

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SOURCES:
- HACKER AND MOORE’S ESSENTIALS OF OBSTETRICS AND GYNECOLOGY
- 428 TEAM BOOKLET
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Physiological and anatomical changes occur during the course of pregnancy to provide a suitable environment for the growth and development of the fetus.

**EARLY CHANGES:**

- Due to:
  - Metabolic demands brought by the fetus, the placenta and the uterus.
  - Increasing levels of pregnancy hormones:
    - **Progesterone:**
      - Synthesized by the Corpus Luteum until day 35, then by the placenta till end of pregnancy
      - Promotes smooth muscle relaxation (gut, ureters and uterus)
      - Raises body temperature
    - **Estrogen (90% estradiol):**
      - Promotes breast and nipple growth, and pigmentation of the areola
      - Promotes uterine blood flow, myometrial growth and cervical softening
      - Increases sensitivity and expression of the myometrial-oxytocin receptors
      - Increases water retention and protein synthesis
    - **Human placental lactogen (hPL):**
      - Structurally and functionally similar to the Growth Hormone (GH)
      - Modifies maternal metabolism to increase the energy supply of the fetus
      - Causes high insulin secretion, yet low insulin peripheral effect (insulin resistance; allowing fatty acids to be utilized instead of the glucose of which is diverted to the fetus)

**LATE CHANGES:**

- Anatomical in nature and are caused by mechanical pressure of the expanding uterus

**SYSTEMATIC CHANGES**

**ALIMENTARY SYSTEM**

**GENERAL**

- Appetite:
• Is generally not changed
• Pica; an appetite for non-nutritive substances (non-food cravings). The suggested causes are:
  - Mineral deficiency such as ‘iron deficiency’
    (Pregnant ladies have higher risk of pica due to low blood levels of iron.
  - Psychological cause on the basis of OCD (non-pregnant pica)

**MOUTH:**

- **Ptyalism:**
  - Drooling, or excessive salivation
  - Happens in those suffering from vomiting and nausea, and is unknown in origin
  - Occurs during the 1st trimester of pregnancy
- **Dentition:**
  - Due to the **hormonal effect** of Progesterone → smooth muscles swell, blood flow increase
  - Is described as:
    - Gums swell, soften and become edematous
    - Teeth become sensitive and easily bleed
    - Complication; it makes the mouth vulnerable to infection; plaque and gingivitis (gingivitis; gum infection)

**STOMACH:**

- **Hormonal effect** of high Progesterone and LOW motilin:
  - Low tone and motility:
    - Gastric → decreased emptying and high residual volume
    - Lower Esophageal Sphincter (LES) → GERD and heartburn
  - High mucus secretion, and low acid secretion → low peptic ulcer disease

**SMALL BOWEL:**

- **Hormonal effect** of high Progesterone:
  - ↓ Motility
  - ↑ Iron absorption and others nutrients’ unchanged.

**COLON:**

- **Hormonal effect** of high Progesterone:
  - ↓ Motility → Constipation → Hemorrhoids
  - Water absorption increase up to 60%, and sodium absorption increase up to 45%.
GALLBLADDER:

- **Hormonal effect** of high Progesterone:
  - ↑ Emptying time
  - ↑ Fasting & residual volume

Biliary cholesterol saturation → stagnation and gallstones formation

LIVER:

- All markers of liver function are generally reduced or low during pregnancy due to the expansion of extracellular fluid.
- Hence serum albumin, transaminases (AST and ALT) and total bilirubin are low compared with the non-pregnant state.
- The only exception is serum alkaline phosphatase (ALP) which is elevated due to ALP of placental origin.
- **Hormonal changes** of raised Alkaline phosphatase:
  - Due to the production from a placental isoenzyme
  - The only liver enzyme that rises (not AST or ALT)

- **Serum Protein Concentrations** changes:
  - Increase in **Coagulation Factors** levels such as Fibrinogen
  - Increase in **Steroid-binding globulin** and so Cholesterol and lipids facilitating glucose sparing for the fetus
  - Increase in **gamma globulins**, but overall globulins levels remain normal
  - Decrease in **Serum Albumin** levels due to Hemodilution (blood volume increase)

- Nausea & Vomiting:
  - Increase due to low stomach tone and ↑ hCG hormone levels
  - **Hyperemesis gravidarum**; (severe vomiting beginning in early pregnancy) frequently occurs in molar pregnancy

RESPIRATORY SYSTEM

GENERALLY

- Major respiratory changes involve 3 factors:
  - Mechanical effect of enlarging uterus
  - Increased total body oxygen consumption; by 20% as:
    - ↓ PCO2
    - ↑ Po2 and pH
    - Other arterial gasses aren’t changed.
  - Respiratory stimulant effect of Progesterone

- Nose; Hyperemic, edematous, stuffiness, epistaxis and polyps may develop

RESPIRATORY MECHANICS IN PREGNANCY

- The resting diaphragm is pushed up to 4cm than the non-pregnant level.
- The chest enlarges in transverse diameter.
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Subcostal angle increases.

As pregnancy progresses, the enlarging uterus elevates the resting position of the diaphragm → less negative intrathoracic pressure → ↓ resting lung volume

LUNG DYNAMICS

- All lung volumes become ↓ except Tidal volume is ↑ by 40%.
- All lung capacities are ↓ except:
  - Inspiratory capacity becomes ↑
  - Vital capacity remains unchanged.
- Respiratory Rate remains unchanged → minute ventilation increases by 40%.
- Hyperventilation due to progesterone and Dyspnea of pregnancy may occur.

DERMAL CHANGES

- The Hormonal effect of Estrogen:
  - Spider nevi
  - Palmar erythema
  - Melanocyte Stimulation

- Stretched skin → Striae gravidum
- Melanocyte stimulation:
  - Darkening nipples and areolae
  - Dark umbilicus and perineum
  - Linea nigra (a dark vertical line that appears on the abdomen during about three quarters of all pregnancies)
  - Malasma or cholasma (a dark skin discoloration that appears on sun-exposed areas of the face)
  - Pigmented nevi
- Hair loss, mostly post-partum, due to the effect of hormones decline of which stops the hairs from falling during pregnancy.
- Separation of rectus muscle (diastasis recti) in the later stages of pregnancy. It is due to the significant pressure from the uterus on the abdominal wall, also, softening of connective tissue due to hormonal changes can also be a contributing factor.

RENAL SYSTEM

ANATOMIC CHANGES IN THE URINARY TRACT

- The urinary collecting system (including calyces, renal pelves – kidneys - and ureters) undergo marked dilatation in pregnancy
- Hormonal effect of Progesterone: produce smooth muscle relaxation in various organs including the ureters.
As the uterus enlarges → partial obstruction of the ureters occurs at the pelvic brim in supine and upright position (high risk of pyelonephrosis and asymptomatic bacteruria).

The right side increases in size more than the left side.

The change in size is called ‘physiological hydronephrosis’.

**RENAL BLOOD FLOW AND GLOMERULAR FILTRATION RATE**

- Renal blood flow and GFR ↑ in 50%, start early in pregnancy, plateau at midgestation and remain unchanged to term.
- High GFR → High creatinin clearance, Glycosuria (common), Aminoaciduria and water-soluble vitamin excretion.
- The elevated GFR is reflected in ↓ Blood urea nitrogen, Serum Creatinine and Serum uric acid.
- Proteinuria > 300 mg in 24 hrs. urine collection is abnormal.
- Vasorelaxation of afferent and efferent arterioles of the renal arteries, induced by relaxin, endothelia and nitric oxide.
- This resulting rise in renal plasma flow accounts for the hyperfiltration
- Plasma concentrations of renin, renin substrate and angiotensin I and II are increased during pregnancy.

**CARDOVASCULAR SYSTEM**

**THE HEART**

- There are both size and position changes which can lead to changes in ECG appearance.
- The heart is enlarged by both chamber dilation and hypertrophy.
- Upward displacement of the diaphragm by the enlarging uterus causes the heart to shift to the left and anteriorly, so that the apex beat is moved outward and upward, and the heart lies more horizontally giving the appearance of cardiomegaly.

**Normal Changes:**
- Systolic ejection murmur
- Exaggerated S1 and S3 gallop
- Mammary soufflé.

**Abnormal Changes:**
- Changed ECG
- Diastolic murmurs
- Changed S2

**PERIPHERAL CIRCULATION**

- Increased Cardiac Output (CO) and Heart Rate (HR) → increased Stroke Volume (SV) and lower extremity venous pressure.
- Low peripheral vascular resistance due to *Hormonal effect* of Progesterone.
**BLOOD PRESSURE**

- The BP in normal pregnancy is never higher than non-pregnant values, but it is lowest in lateral decubitus position and highest when seated.
- The CO is dependent on maternal position.
- Optimal CO, is when the mother is in the left lateral position
- Lowest CO is when supine, which may result into "supine hypotensive syndrome"

**HEMATOLOGICAL SYSTEM**

**PLASMA VOLUME**

- Increase by 10-15% at 6-12 weeks of gestation
- Expands rapidly until 30-34 weeks, and the total gain at term is a 30-50% more expansion from the non-pregnant state
- Acute excessive weight gain is commonly due to edema

**RED CELL VOLUME (MASS)**

- RBC mass increases by 31% (if with folate and iron supplementation, and if not, it only increases to 13%)
- The discrepancy between the rate of increase of plasma volume and red cell mass results in a relative ‘hemodilution’ or ‘physiological anemia’ with the hemoglobin concentration, hematocrit and red cell count all low (particularly in the second trimester)
- ESR increase up to 4-fold in pregnancy
- The mean daily requirement of elemental iron for pregnant woman is 3.5 mg. Daily iron supplementation of 60 mg prevents development of iron deficiency anemia.

**TOTAL WHITE CELL MASS**

- Neutrophil polymorphonuclear leucocytes increase → WBC count increase
- A further massive *Neutrophilia* occur during labor
- Eosinophils, basophils and monocytes remain relatively constant (eosinophil will profoundly decreased during labour; being virtually absent), while lymphocyte count remain constant
- The lymphocyte function and cell-mediated immunity are profoundly depressed → rise to a lowered resistance to viral infections

**PLATELETS**

- Slight decrease that they remain in normal range
- The function remain unchanged

**CLOTTING FACTORS**

- Pregnancy is a hypercoagulable state
- Most clotting factors increase including *Fibrinogen*
- Thromboembolism is the number one cause of maternal mortality.
- The risk of having Thromboembolism is higher during puerperium than in pregnancy.
ENDOCRINE SYSTEM

EFFECT ON THE THYROID

SIZE OF THE GLAND

- Maternal thyroid gland enlarges due to high demand in pregnancy
  - The high renal clearance of iodine result in a relative iodide deficiency
  - The thyroid respond by tripling its iodide uptake from the blood → follicular enlargement

HORMONAL CHANGES

- **Hormonal Effect of Estrogen** causes the Thyroid-binding globulin (TBG) to be doubled by the end of the first trimester.
- As a result; total and bound T3 and T4 increases, while others remain unchanged including free T3 and T4 (rise early in pregnancy, then fall post-partum)
- Thyroid-stimulation Hormone may decrease slightly in early pregnancy but remain within the normal range

- Iodine, anti-thyroid drugs, and long-lasting thyroid stimulators (LATS) or antibodies associated with graves disease (Thyroid stimulating immunoglobulin, Thyroid releasing hormone TRH) can cross the placenta

EFFECT ON THE ADRENAL GLAND

- Adrenocorticotropic hormone (ACTH) and plasma cortisol, aldosterone and deoxy-corticosterone levels are both elevated from 3 months gestation to delivery.
- Unlike thyroid hormones levels, the mean unbound level of cortisol is elevated in pregnancy.
- There’s some loss in the diurnal variation (a concentration characterized from the non-pregnant state)

EFFECT ON THE PANCREAS

- Hypertrophy, Hyperplasia and Hypersecretion of Beta-cells.
- **Maternal response to feeding**; are a prolongation of:  
  - Hyperglycemia  
  - Hyperinsulinemia  
  - Hypertriglyceridemia.
- **Maternal response to fasting**; is accelerated starvation that could result in "Exaggerated Starvation Ketosis".
- Insulin & Glucagon can't cross the placenta BUT Glucose, Ketones, Amino acids, free fatty acids can.
- There’s a peripheral tissue resistance to insulin is that suggested by:
  1. Increased insulin response to glucose.
  2. Decreased glucose uptake peripherally.
  3. Decreased glucagon response.
Insulin resistance in pregnancy caused by:
1) Human placental lactogen (HPL).
2) Placental insulinase.
3) Increased free cortisol and progesterone.

**EFFECT ON THE PITUITARY GLAND**

- Enlarges mainly due to changes in the anterior lobe (↑size by 111%).
- *Hormonal effect* of Estrogen; stimulation to lactotrophes → increased prolactin levels
- Gonadotrophin secretion is inhibited while plasma ACTH levels are high.
- The posterior lobe secretes oxytocin during the first stages of labour and during suckling.
- Sheehan's syndrome may happen due to severe PPH (postpartum hemorrhage) and it causes a failure to lactation (its characteristic)
ANEMIAS IN PREGNANCY

DEFINITION

- A reduction in the concentration of hemoglobin in the blood to < 10 g/dl (in non-pregnant, the level of anemia is < 12 g/dl).
- There should be no change in MCV or MCHC in normal pregnancies.
- Physiological anemia result after expansion in plasma volume that precedes the RBCs count, and that’s different than a pathological anemia that is with a Hb < 10 g/dl.

IRON DEFICIENCY ANEMIA

DEFINITION

- The commonest cause of anemia in pregnancy (90% of cases)
- The fetus is always saved on the expense of maternal Fe stores, hence the predisposition.

MANAGEMENT

- Often asymptomatic and detected on screening
- Routine CBC:
  - At the time of booking
  - At 32 weeks
- Done for follow-up if the patient is already on therapy
- CBC is done at 32 weeks to make sure that the patient has a decent Hb count before going to labour

DIAGNOSIS AND INVESTIGATIONS

- All the parameters are needed to diagnose; CBC with red-cell indices.
- Blood smear is important to exclude Sickle Cell Anemia
- Iron Profile: TIBC (total iron binding capacity; transferrin) is high, while Serum Fe and Serum Ferritin are low.
- Red-cell indices: low MCV and low MCHC

TREATMENT

- Iron Replacement:
  - Orally; iron tablets
  - Parenteral; injections (some develop anaphylactic shock)
Resistance to therapy requires a dietary diary to specify its intake with malabsorbing agents such as milk and tea or low intake of vitamin C (increases absorption).

If a patient is still with severe anemia and is close to labour, transfusion is needed and so blood profile should be taken.

**CAUSES**

- Lack of intake
- Malabsorption syndromes; IBD, IBS, celiac disease, etc.
- Losses: hemorrhoids, hematuria, chronic blood loss.

**SICKLE CELL DISEASE**

**DEFINITION**

- It is an inherited autosomal recessive disorder where the red cell contains Hb(s) instead of normal Hb. which causes the sickling. (SS = disease S = carrier)
- This disease is common in the Southern region, e.g. Gizan, Asir, Najran
- Carriers don't manifest the disease, but might pass it to offspring
- Diagnosis is made in childhood, and it is rare to make a new diagnosis in pregnancy.

**RISKS AND COMPLICATIONS IN PREGNANCY**

- ↑ Maternal mortality + morbidity:
  - HTN
  - Pre-eclampsia
  - Eclampsia
- ↑ Abortion
- Crisis attacks are more common in pregnancy
- High risk for C-section delivery secondary to fetal distress
- ↑ Perinatal mortality and morbidity:
  - Prematurity
  - IUFD and IUGR
  - PROM and PREM. LABOUR

**CLINICAL FEATURES OF SICKLING**

- Hemolytic anemia
- Painful crises (Sickle cell crisis; Sickling of red cells with Hb.S → Ischemia and infarcts of different organs → Pain)
- Hyposplenism (chronic damage to the spleen results in atrophy)
- Increased risk of infection (UTI, pyelonephritis, pneumonia, puerperal sepsis)
- Avascular necrosis of bone
- Increased risk for thromboembolic states (pulmonary embolism and strokes)
- Acute chest syndrome (fever, chest pain, tachypnea and pulmonary infiltrates)
- Iron overload leads to cardiomyopathy
- Hepatosplenomegaly
PHYSIOLOGICAL CHANGES & DISORDERS IN PREGNANCY

- Renal medullary damage
- Ventricular hypertrophy
- Leg ulcers and sepsis
- Pulmonary infarctions

MANAGEMENT

- It should be a multidisciplinary care between the obstetrician and the hematologist
- Iron-chelating agents should be stopped before pregnancy (if there’s iron overload, arrange for maternal echo).
- Folic acid should be given (5 mg/day) and penicillin prophylaxis for hyposplenism.
- Monitor Hb and HbS. percentage and arrange transfusion if necessary (may have red cell antibodies from multiple transfusions)
- Transfusions never let the patient reach our normal levels, but they have their own targets.
- Transfusion is not made unless there are sickling symptoms
- Screen for urine infection in each visit.
- Early treatment of infections (UTI and pneumonia) is advisable as they cause acute crisis.
- IV hydration and analgesia
- Close fetal monitoring NST (non-stress test), BPP (biophysical profile) and US for growth.
  (A BPP test may include a nonstress test with electronic fetal heart monitoring and a fetal ultrasound. The BPP measures the fetal heart rate, muscle tone, movement, breathing, and the amount of amniotic fluid)
- Fetal monitoring is made to ensure adequate hydration and avoid hypoxia for vaginal delivery.

DIAGNOSIS:

- History taking, physical examination and labs
- Sickling test for screening
- Hb electrophoresis for confirmation

DELIVERY CARE

- Vaginal delivery is encouraged to avoid blood loss, but C-section rate is high due to common pelvic deformity.
- Continuous fetal monitoring should be initiated due to impaired placental function
- Prenatal counseling, patient education and partner electrophoresis and diagnosing is important

THALASSEMIA

DEFINITION

A group of genetic conditions leading to impaired production of the normal globulin chains (alpha and beta) resulting in red cells with inadequate hemoglobin content (ineffective erythropoiesis and hemolysis → anemia)
**TYPES**

**ALPHA THALASSEMIA**
- Caused by defects in 1-4 of the alpha-globulin genes
- Alpha-thalassemia Trait has 2-3 normal alpha genes, and women are usually asymptomatic but may become anemic in pregnancy
- Alpha-thalassemia major (Hb F/Barts) has no functional alpha genes and is incompatible with life (fetuses are often hydropic and born prematurely, while the pregnancy comes accompanied with severe onset pre-eclampsia)

**BETA THALASSEMIA**
- Beta-thalassemia trait has one defective gene and women are asymptomatic, but may become anemic in pregnancy
- Beta-thalassemia major has two defective genes and women are usually transfusion dependent.
- Women with major beta thalassemia complain of:
  - Iron overload
  - Delayed puberty
  - Subfertility and only few pregnancies have been reported

**OTHER TYPES OF ANEMIA**

**ANEMIA OF ACUTE OR CHRONIC BLOOD LOSS**
- Comes with bleeding or chronic blood diseases
- SLE, Chronic renal failure and dialysis are one of the major diseases

**MEGALOBLASTIC ANEMIA**
- Caused by Folic Acid (not accompanied with neural symptoms) and/or Vitamin B12 (accompanied with neural symptoms).
- Folic acid and Vit.B12 are major causes to low erythropoietin and so; anemia.

**THYROID DISEASES IN PREGNANCY**

**HYPERTHYROIDISM AND THYROTOXICOSIS**
Occurs in 1:500 pregnancies and the most common cause is Graves disease (95%)

**GRAVES DISEASE (AUTOIMMUNE THYROIDITIS)**
- An autoimmune disease characterized by the production of TSH receptor stimulating antibodies.
- Most women have been diagnosed before pregnancy and may be on treatment
Many symptoms and signs occur in pregnancy, and most discriminatory are:

- Weight loss
- Tremors, insomnia and irritability
- Persistent tachycardia
- Eye signs of exophthalmos

Diagnosis: low TSH and high free T4 or fee T3 levels with the antibodies

Treatment:
- Anti-thyroid drugs; Carbimazole and Propylthiouracil crosses the placenta → causes fetal hypothyroidism and goiter, hence; lowest dose of the drugs are used
- Thyroidectomy is safely done in pregnancy
- Radioactive I$_2$ is contraindicated (anything radioactive is contraindicated in pregnancy and breast feeding)

Effect of thyrotoxicosis on pregnancy:
- Maternal and fetal outcome is good if the disease is controlled
- Untreated or poorly controlled thyrotoxicosis is associated with subfertility (amenorrhea due to weight loss), high risk of miscarriage, IUGR and premature delivery

HYPOTHYROIDISM

- It complicates in 1% of pregnancies
- Most cases have been diagnosed previous and patients are on replacement therapy. New diagnosis cases are rare.
- The commonest cause is autoimmune that may be associated with other autoimmune conditions
- Effect of hypothyroidism on pregnancy:
  - Untreated hypothyroidism is associated with anovulatory infertility
  - Severe or untreated hypothyroidism in pregnancy is associated with increased risk of miscarriage, fetal loss, pre-eclampsia and low birth weight.
  - The fetus requires maternal T4 for normal brain development before 12 weeks, after this time T3/T4/TSH do not cross the placenta (inadequate replacement may result in reduced IQ in the offspring)
- Dose monitoring:
  - Pregnancy doesn't affect the therapeutic dose UNLESS their dose was already inadequate; hence, they need to control it before getting pregnant
  - The dose is monitored through TSH to adjust the dose when needed.

DIAGNOSING GOITER

We should detect the normal thyroid changes in pregnancy (physiological goiter due to high vascularity in pregnancy should be differentiated from pathological goiter)