Reviewed By
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Physiological Changes in Pregnancy

Objectives:

- → Symptoms and physical findings of each organ system.
- → Physiologic versus pathologic changes.
- → Diagnostic tests and interpretations during physiological changes.
- → Discuss the maternal physiologic and anatomic adaptation to pregnancy related to the following: Cardiovascular, Respiratory, Renal, Endocrine systems and Weight gain.
- → Discuss the properties, functions and interactions of pregnancy related hormones.
- → Describe the mechanisms of maternal and-fetal transfer of substances across the placenta.
- → Describe the placental transfer of oxygen and CO2 of the fetal circulation.
- → Describe components of the fetal circulation.
- → Explain how the fetal circulation differs from the adult circulation.

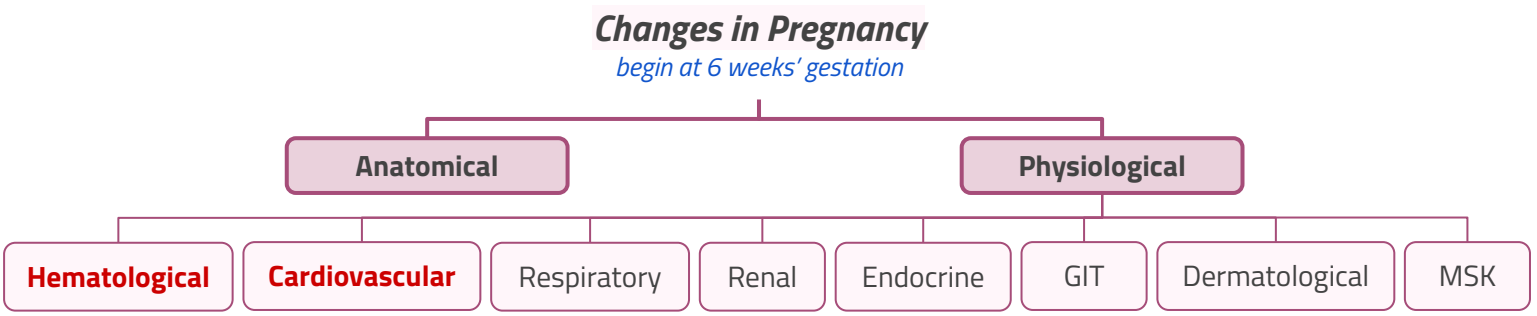
- → Slides
- → Important
- → Golden notes
- → Extra
- → Doctor's notes
- → Previous Doctor's notes
- → Reference

Kaplan Video

Editing File

Physiological Changes in Pregnancy

Changes in Pregnancy:



1. Hematological Changes in Pregnancy

Hypercoagulability:

→ Pregnancy is a **hypercoagulable** state → reduces the risk of intrapartum blood loss (*remember this*).
→ Estrogen & vascular stasis (in case of IVC compression by gravid uterus).
  → We don't have to give prophylactic anticoagulants to everyone.
  → Prophylactic anticoagulants given to:
    → Immobility (admission - bed rest - placental anomalies).
    → History of thrombosis.
  → IVC compression management? turn the mom on to her left side)
→ ↑ **risk for thromboembolic diseases (DVT – PE –Stroke):**
  → ↑ fibrinogen (**DIC:** normal or borderline low).
  → ↑ all coagulation factors **except** II, V, XII (↑ **D-dimer → not used diagnostically in pregnancy**).
  → ↓ protein S & sensitivity to Anti-Protein C (APC).
  → ↓ platelets (still within normal range 150 - 400) & factor XI and XIII.
    → **Q:** is a platelet count of 90 or 130 physiological ? No.
  → ↑ in WBC (still within normal range), **13 and above is pathological**.

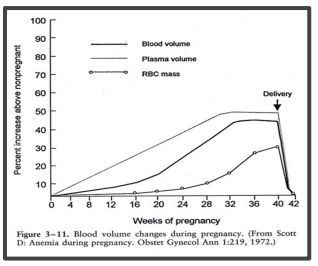
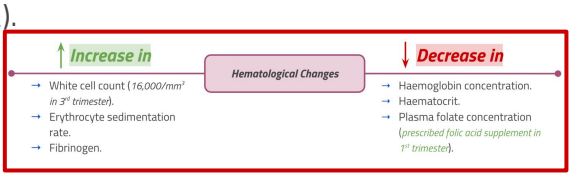


Figure 3–11. Blood volume changes during pregnancy. (From Scott D: Anemia during pregnancy. Obstet Gynecol Ann 1:219, 1972.)

Hemoglobin & Physiological Anemia of Pregnancy:

→ ↑ **Plasma volume:** 50 -70 % (**hemodilution** (*physiological*) → ↑ plasma volume + ↓ haemoglobin).
  → Extra reserve → tolerate hemorrhage & blood loss up to 1000 cc (*kills a healthy 18 y.o male*).
  → **Beginning by:** 6th week.
  → **Maximum plasma volume:** 30 weeks, even greater with multiple fetuses.
  → ↑ Plasma volume → ↓ hematocrit (at 30 – 34th wks) → **dilutional anemia** (*Hgb rarely < 11 g/dL*).
→ **Normal pregnancy Hemoglobin (↓Hgb): 10 - 14 g/dL**.
  → **Initially:** 12-16 g/dL initially (*same*).
  → **Later with ↑ in demand:** drop down to 10 g/dL (still be normal physiological anemia).
    → At least should be 10 in case the pregnant lady needs c-section.
  → **Lowest Hgb:** 28 - 30 weeks.
→ **Normal pregnancy Hematocrit (↓ Hct):** 38 - 47 % (15% ↓).
  → **Later:** 32 - 42 %.
→ ↑ **RBC mass: 20 - 35 %**.
  → **Beginning by:** 8 - 10th or 12th week.



2. Cardiovascular Changes in Pregnancy

Normal Changes of Heart Sounds in Pregnancy:

01 ↑ loudness S1 & S2

02 ↑ splitting of mitral & tricuspid S1 components.

03 No constant changes in s2.

04 Loud **s3** by 20 weeks' (5th month).

05 S4 in <5% of pregnant women.

06 **Systolic ejection murmur** in left sternal border (>95%) → disappear after delivery
Hyperdynamic state → ↑ cardiac output + ↑ plasma volume

07 **Transient diastolic murmur** (20%)
In 2nd trimester → could be pathological → do workup

08 ↑ mammary blood flow → **continuous murmurs** (10%) (during pregnancy)

Cardiovascular Changes:

01 ↑ **heart rate:** 10 - 20%.
- → **End of 1st trimester:** 30%.
- → High **normal** range 90 -100 bpm.
- → **Common complain:** palpitations.
- → **3rd trimester:** +20 bpm.

02 ↑ **stroke volume:** 10%.

03 ↑ **cardiac output:** 30 - 50%.
- → **Major increase:** by 20 weeks

04 ↓ **mean arterial pressure:** 10%.
- → **Never normally** ↑ in pregnancy.
- → Diastolic falls > systolic ~15 mmHg.
- → Early in 1st trimester.
- → **Lowest:** 24 – 28 weeks.
- → Gradually ↑ toward term, but never to prepregnancy baseline.

05 ↓ **peripheral resistance:** 35%.
- → Contributes to hypercoagulable state.
- → **Lowest:** 20 weeks.
- → ↑ progesterone → ↓ vascular tone → ↓ peripheral vascular resistance → ↓ afterload.

Blood Pressure & Eclampsia: *skipped by the doctor*

- → **Be careful! eclampsia and preeclampsia** → ↑ morbidity and mortality.
- → **Mid-trimester:** slight ↓ blood pressure '*still in normal range*' → postural hypotension + pop-fainting.
- → **Labour:** pain → a bit ↑ blood pressure.

2. Cardiovascular Changes in Pregnancy

Normal Physiology of Pregnancy that Mimic Heart Disease:

Signs

- → **Peripheral edema:**
  - → Uterus compresses the lymphatic vessels.
  - → May be pathological.
  - → Compare both sides and monitor progress.
  - → **Advice:** rise leg → circulate blood and lymphatics.
- → JVP.
- → **CVP:** unchanged.
- → **Femoral venous pressure (FVP):** ↑ 2 - 3 by 30 weeks.
- → **Arrhythmia:** pathological not a physiological finding.

Symptoms

- → Reduced exercise tolerance
- → Dyspnea

Auscultation

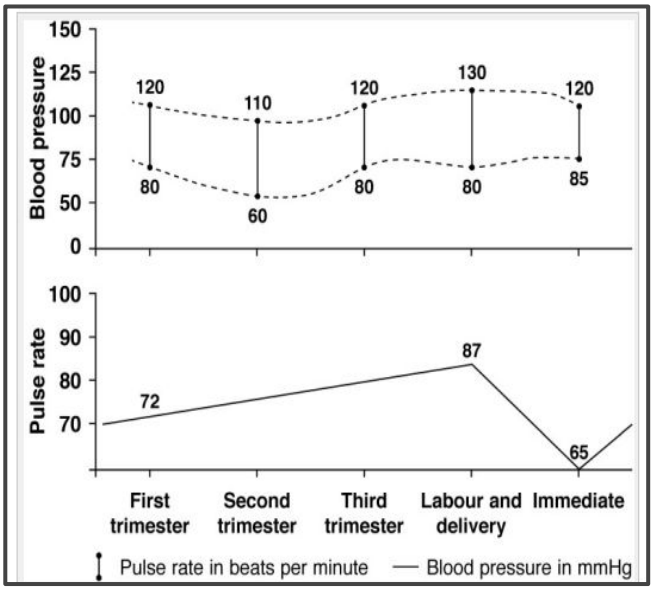
- → S3 gallop
- → **Systolic ejection murmur**

Chest X-Ray

- → Change in heart position & size
- → ↑ vascular markings

EKG

- → Nonspecific ST-T wave changes
- → Axis deviation
- → LVH



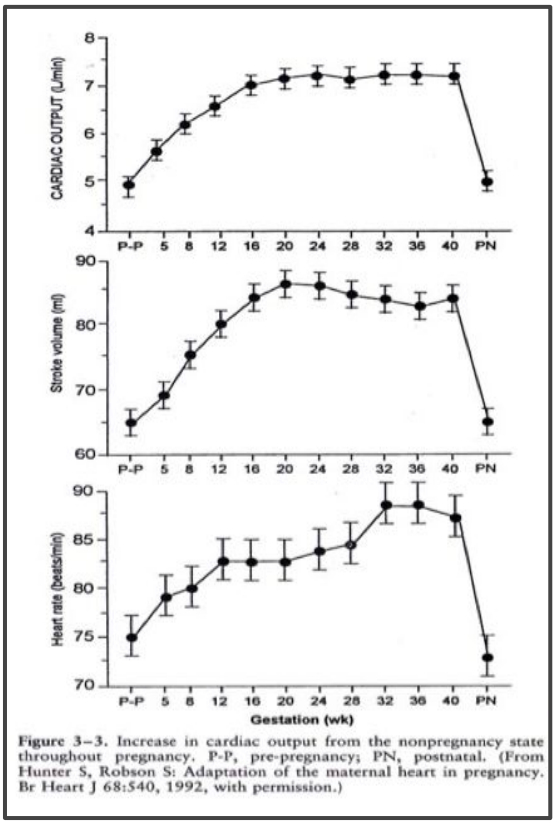


Figure 3–3. Increase in cardiac output from the nonpregnancy state throughout pregnancy. P-P, pre-pregnancy; PN, postnatal. (From Hunter S, Robson S: Adaptation of the maternal heart in pregnancy. Br Heart J 68:540, 1992, with permission.)

3. Renal Changes in Pregnancy

Renal Changes:

1

Filter Changes

1. Renin:

- → **Stimulated by:** progesterone
- → **Made by:** placenta
- → **Physiology:** Angiotensinogen → Angiotensin I → Angiotensin II → Aldosterone
- → **Aldosterone affects distal tubule:**
  - → Net **absorption of Na^+**.
  - → **Excretion of K^+**.
  - → **Water retention:** 6 - 8 L.

2. ↑ Renal Blood Flow (50/60 - 75%):

- → **GFR:** ↑ 50%.
- → ↓ Albumin → ↓ colloid oncotic pressure → edema of lower limbs.
- → Pregnancy → ↓ resistance in afferent & efferent arterioles of renal arteries (*vasorelaxation*) → ↑ renal plasma flow → hyperfiltration.
  - → **Induced by:** relaxin - endothelin - nitric oxide.

2

Urinary Tract Changes

- → **Ureteral dilation (hydroureter):**
  - → Progesterone → relaxation of smooth muscles of renal pelvis & ureters.
  - → Later exacerbation by uterine obstruction.
  - → Urinary stasis → more prone to infections.
  - → Right side dilates more than the left side in 90% of patients.
- → **Pelvis and calyces dilation**
- → ↑ **kidney size:** + 1.5cm, which doesn't reverse until 3 months postpartum.

3

Renal Function Changes

- → ↑ clearance of most substances.
- → ↓ plasma creatinine, urea and urate by 25%.
- → **Glycosuria (normal):** ↑ glomerular filtration → overload of glucose carrier (*responsible for resorption*).

4. Respiratory Changes in Pregnancy

Respiratory Changes:

1 Mechanical

→ **Diaphragmatic excursion:** diaphragm will change in position (4 cm upwards) and shape.
→ Gravid uterus → upward displacement of intraabdominal contents against the diaphragm → ↓ residual volume (RV) up to 20% by 3rd trimester → less negative intrathoracic pressure + ↓ functional residual capacity (FRC) + no change in vital capacity (VC)

2 Consumption

→ ↑ oxygen need/requirements/demand.
→ ↑ O_2 consumption by 15 - 20% .
  → 50% of this increase is required by the uterus.
→ Despite ↑ oxygen requirements, ↑ Cardiac Output + ↑ alveolar ventilation → O_2 consumption > O_2 requirements → ↓ arteriovenous oxygen difference + ↓ arterial PCO_2.

3 Stimulation

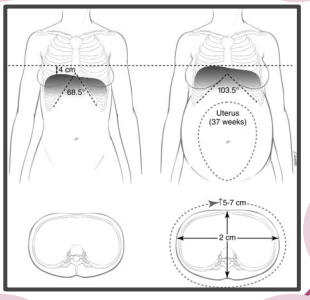
→ **Progesterone:**
  → Progesterone stimulates the respiratory centers in brain → hyperventilation (to eliminate fetal CO_2 more efficiently) → physiological, chronic compensated respiratory alkalosis → renal compensatory bicarbonate excretion → final maternal blood pH of between 7.40 and 7.45.

01 ↑ PO_2.

02 ↑ in subcostal angle, & chest circumference and diameter.

03 ↑ blood supply → mucosal hyperemia.

04 **Mild respiratory alkalosis**.
→ **PCO_2:** 30 - 40 mmHg.
→ **pH:** 7.40 - 7.45
  → **Compensation:** ↑ renal loss of bicarbonate → alkalotic urine.



05 ↓ PCO_2.

06 ↓ total lung capacity by 15%.

07 **Tidal volume (Vt):** +30 – 40%.
→ The only lung volume that doesn't ↓ with pregnancy.

08 **Minute ventilation (Ve) :** +30 – 40%.
→ Causes respiratory alkalosis.

5. Endocrine Changes in Pregnancy

Endocrine Glands:

1 Pituitary Gland

→ Placenta → ↑ estrogen and progesterone → ↓ FSH and LH.
→ ↑ ACTH + thyrotrophin + melanocyte hormone (*due to* ↑ *ACTH*, *result in pigmentation*) + prolactin.
→ **Prolactin:** ↑ until 30th week of pregnancy, then more slowly to term.
→ Estrogen → lactotroph cell hyperplasia and hypertrophy → 3x or up to 40% ↑ pituitary size (*physiological*) → susceptible to ischemic injury (Sheehan syndrome) from postpartum hypotension.

2 Adrenal Gland

→ 2-3x ↑ total corticosteroids progressively to term → ↑ tendency to develop abdominal strine + glycosuria + hypertension.
→ CRH from placenta stimulates ACTH → ↑ free plasma cortisol → explains the stria.

3 Thyroid Gland

→ ↑ ability of kidneys to excrete → ↓ plasma iodine levels → colloid deposition → 2x ↑ thyroid gland size.
→ Oestrogen → ↑ secretion of thyroxine in binding globulin → ↑ T_3 and T_4 levels.
→ This rise will **not** indicate hyperthyroidism.
→ Why? By sharing the common a subunit with HCG it will give falsely high levels.
→ ↑ TBG → ↑ total T_4 and T_3 (*during the 1st trimester*).
→ **Unchanged free T_4 and T_3 levels** → never measure the total in pregnant ladies.
→ HCG suppresses TSH
→ ↑ TIBG (via liver).

4 Pancreas

→ **Carbohydrate metabolism:** insulin resistance.
→ Test for gestational diabetes after 24 week.
→ ↑ human placental lactogen + progesterone + prolactin + cortisol + placental cytokines → progressive insulin resistance during pregnancy (insulin antagonist).

6. Gastrointestinal Changes in Pregnancy

Gastrointestinal Tract:

01 **Progesterone → slow GI motility.**
- → Constipation (***Treatment:*** *stool softeners - motility agent*).
- → Early satiety.
- → ↑ stomach volume + upward displacement by the gravid uterus → aspiration pneumonia with general anesthesia at delivery.

02 **Progesterone → relaxation/ ↓ tone of lower esophageal sphincter (LES) → GERD & heartburn.**
- → **Treatment:** PPI

03 **Nausea & vomiting, often proportional to HCG level.**
- → Causes of high HCG level? molar pregnancy - twin pregnancy.
- → **Treatment:** ondansetron

04 **Liver & gallbladder:**
- → Biliary stasis – cholesterol saturation – prolonged emptying time → more stones.
  - → If you have to remove the gallbladder as urgent or Emergent do it in 2nd trimester.
- → Bile salt buildup → itching.
- → Coagulation factors.
- → ↑ binding proteins (thyroid, steroid, vitamin D).

05 **Progesterone → digestive system slows.**

06 **Ptyalism:** ↑ salivation.

07 Dilated blood vessels + ↑ pressure in veins → **hemorrhoids**.
- → Progesterone → dilated blood vessels.
- → Uterus presses against the pelvic veins and vena cava → impaired venous return.
- → Never ever intervene unless you have complications (strangulation - thrombosis)!

08 **Displacement of the stomach and intestines.**

09 **Appendix can be displaced to reach the right flank.**

10 **Hormonal and mechanical factors → delayed gastric emptying and intestinal transit times.**

11 **Reflux of secretions → pyrosis.**

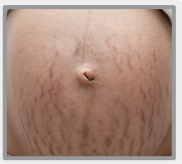
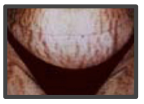
12 **Vascular swelling of the gums.**

7. Dermatological Changes in Pregnancy

Dermatological Changes:

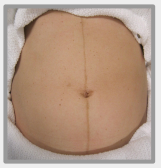
Striae gravidarum

Stretch Marks
→ In genetically predisposed women.
→ **Location:** abdomen & buttocks.

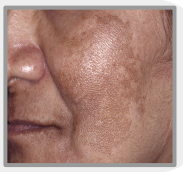
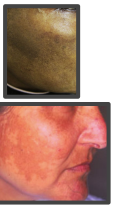
Linea nigra

→ ↑ pigmentation.
→ **Location:** lower abdominal midline from the pubis to the umbilicus.




Chloasma or melasma gravidarum

→ Blotchy pigmentation of the nose and face.

→ ↑ skin vascularity → **spider angiomata** & **palmar erythema**.
→ **Chadwick sign:**
  → Bluish or purplish discoloration of the vagina and cervix.
  → **Cause:** ↑ vascularity.

8. Musculoskeletal Changes in Pregnancy

Musculoskeletal Changes:

Musculoskeletal consequence that ensues result of hormonal changes and weight gain (28 lbs ave) include:

01
2x ↑ force across a joint.

02
Relaxin (*placenta - produced hormone*) → joint laxity in anterior & posterior longitudinal ligaments of lumbar spine → put strain on the lumbar spine.

03
Widening + ↑ mobility of sacroiliac joints and pubic symphysis → facilitate baby's passage through birth canal.

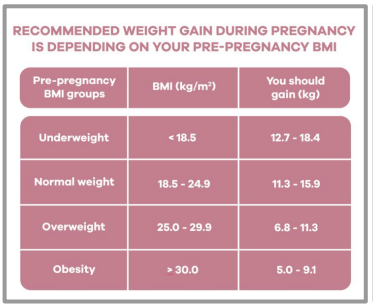
04
Significant ↑ in anterior tilt of pelvis + ↑ use of hip extensor, abductor, and ankle plantar flexor muscles.

9. Weight Changes in Pregnancy

Weight Changes:

Where do the pregnancy Kilos go?	
Maternal stores of nutrients and muscle development	3 Kg
Increased body fluid	2 Kg
Increased blood	1.5 - 2 Kg
Breast growth	600g
Enlarged uterus	1 Kg
Amniotic fluid	1 Kg
Placenta	600g
Baby	3.4 - 4 Kg
Total	**11 - 16 Kg**

→ ↑ **weight:** approximately 12.5 kg at term.
  → **1st trimester:** 1 kg.
  → **2nd trimester:** 5 kg.
  → **3rd trimester:** 5 kg.
→ Main ↑ occurs in the 2nd half of the pregnancy (**0.5 kg/week**).
→ No change in weight → check the baby's growth!
→ Not all numbers are important, just know that the total is 11 - 16.



10. Anatomical Changes in Pregnancy

Anatomical Changes:

A. Breast Changes | **B. Genital Tract Changes**

Uterus

→ **Uterine muscle length:** 15x ↑ than pre-pregnancy.
→ **Uterine weight:** ↑ 50 g (before pregnancy) to 950 g (at term).
  → **Early weeks of pregnancy:** growth by hyperplasia (*more*) + hypertrophy (*partially*).
  → **By 20 weeks:** growth ceases → uterus expands by distension.
  → **First half of pregnancy:** hypertrophy of uterine blood vessels → increasingly coiled in but no further growth after that.
→ **Lower uterine segment:** part of the lower uterus and upper cervix lying between the line of attachment of the peritoneum of the uterovesical pouch superiorly and the histological internal os interiorly.

Cervix

→ Softer & swollen → columnar epithelium of cervix is exposed to vaginal secretions.
→ **Last week of pregnancy:** prostaglandins act on collagen fibres → leukocytes release collagenase → break down collagen → cervix becomes softer & dilatable (*ripening of cervix*).

Vagina

→ Thicker vaginal mucosa.
→ Vaginal muscle hypertrophy.
→ Alteration in the composition of the connective tissue → vagina dilates more easily to accommodate fetus during delivery.
→ Oestrogen → desquamation of superficial vaginal mucosal cells + ↑ vaginal discharge when pathogenesis enter vagina (*candida - trichomonas*) → flourish rapidly.
  → Progesterone + estrogen → ↑ vaginal blood supply → ↑ bartholin gland secretions.

Summary

Physiological Changes in Pregnancy:

Hematology:

1. Hypercoagulable state
2. → ↑ ~25% RBC mass
   → ↑ ~50% plasma volume
   → Dilutional *physiological* anemia
   → Hg > 10 with no symptoms
3. ↑ WBC & ESR
4. **Coagulation profile changes:**
   → ↑ factors 6,7,10
   → ↑ fibrinogen
   → ↓ protein C & S

Cardiovascular:

04 **Normal changes in heart sounds:**
→ Loud S1 & S2
→ Systolic murmurs that disappear after delivery

05
→ ↑ heart rate (20%)
→ ↑ stroke volume (10%)
→ ↑ cardiac output (50%)

06 ↓ peripheral vascular resistance → postural hypotension.

Other:

Other

- ↑ O_2 consumption
- Glucosuria
- → ↑ total T_3 & T_4
  → Unchanged free T_3 & T_4
- ↑ insulin resistance.

Quiz

Question 1:

→ **In normal pregnancy:**

A. Blood pressure falls in the second trimester.
B. Plasma volume decreases throughout gestation.
C. There is a reduction in erythrocyte production.
D. 50 per cent of women have a transient diastolic murmur.
E. There is an increase in the number of polymorphonuclear leukocytes.

Question 2:

→ **Maternal effects on the physiology of the kidney include:**

A. There is a 40 per cent increase in renal blood flow.
B. There is an increase in the glomerular filtration rate.
C. The urea and creatinine are higher than the non-pregnant state.
D. The upper limit of protein excretion in pregnancy is 0.6 g per day.
E. The kidneys increase in size.

Question 3:

→ **You are called in to evaluate the heart of a 19-year-old primigravida at term. Listening carefully to the heart, you determine that there is a split S1, normal S2, S3 easily audible with a 2/6 systolic ejection murmur greater during inspiration, and a soft diastolic murmur. You immediately recognize which of the following?**

A. The presence of the S3 is abnormal.
B. The systolic ejection murmur is unusual in a pregnant woman at term.
C. Diastolic murmurs are rare in pregnant women.
D. The combination of a prominent S3 and soft diastolic murmur is a significant abnormality.
E. All findings recorded are normal changes in pregnancy.

Answer Explanation

A+E	B+E	C
1	2	3

Quiz

Question 1:

→ **What is the skin pigmentation on face called during pregnancy?**

A. Chloasma
B. Colostrum
C. Linea nigra
D. Striae gravidarum

Question 2:

→ **What will be the weight of uterus during pregnancy by full term?**

A. 50 gms
B. 100 gms
C. 500 gms
D. 1000 gms

Question 3:

→ **Which of the physiological changes are expected during pregnancy?**

A. Decreased plasma volume
B. Decreased minute ventilation
C. Increase in fibrinogen
D. Increase in glucose utilization

Question 4:

→ **Thromboembolic disease in pregnancy?**

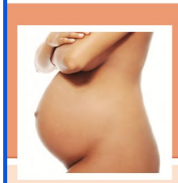
A. Caused by a combination of increased venous capacitance, venous stasis by uterine compression and hypercoagulable state due to increased factors and relative or absolute decreased in proteins C & S.
B. Treated in the standard way with heparin, followed by coumadin
C. Should prompt evaluation with dimers when suspected.
D. Contraindication to thrombolysis.

Answer Explanation

1	2	3	4
A	D	C	A

Reference

CHAPTER 5



Endocrinology of Pregnancy and Parturition

JOSEPH C. GAMBONE • CALVIN J. HOBEL

CLINCAL KEYS FOR THIS CHAPTER

- The hormonal and nonhormonal changes that occur during pregnancy and parturition are regulated through a physiological mechanism referred to as the fetoplacental unit. A series of hormones and transmitters are produced by each of the components of this unit, and they have multiple effects within and between the fetus, the placenta and the mother.
- The fetal component of the fetoplacental unit plays the major role in the regulation of pregnancy and parturition. Most of the activity in the fetal component takes place in the fetal adrenal gland which is larger than the fetal kidney by mid-gestation. The fetal zone of the fetal adrenal gland primarily secretes androgens during fetal life and these androgens act as precursors for estrogen production in the placenta. The overall role of the fetal adrenal is not completely understood.
- The placental trophoblasts are the source of human chorionic gonadotropin (hCG), which "rescues" the corpus luteum very early in pregnancy. The placenta also produces large amounts of steroid and peptide hormones. Because the placenta lacks the enzyme 17α-hydroxylase, it cannot convert progesterone to estrogen. The placenta instead uses androgens from the fetal adrenal as precursors for the production of estrogens that are needed to maintain the pregnancy. In addition to estrogens, progesterone and the corticosteroid, cortisol, are produced in the placenta. Peptide hormones include human placental lactogen (hPL), corticotropin-releasing hormone (CRH), and prolactin. Other important hormones and transmitters include oxytocin, relaxin, prostaglandins, leukotrienes, and parathyroid hormone–related peptide.
- Maternal adaptation and regulation of pregnancy and parturition start with the secretion of 17-hydroxyprogesterone (17-OHP) from the ovarian corpus luteum. If the maternal ovary is deficient in progesterone production, the pregnancy is likely to miscarry. Placental function assures adequate amounts of estrogen (mostly estriol or E3) to increase uterine blood flow for uterine growth, and progesterone to maintain the quiescent state of the uterus throughout most of the gestational period. The absence of myometrial gap junctions facilitates the action of progesterone.
- Labor (which initiates the parturition process) is a release from the state of functional uterine quiescence maintained during pregnancy. This quiescence is due, in large part, to the lack of gap junctions before the onset of labor and the actions of progesterone. Three additional phases of parturition follow the first phase of quiescence, as follows. Phase 1: activation is initiated by uterine stretch and fetal hypothalamic-pituitary-adrenal (HPA) activity. Phase 2: stimulation most likely begins with placental production of CRH. This phase continues with cervical ripening, uterine contractility, and decidual/fetal membrane activation. Phase 3: involution involves expulsion of the fetus with a dramatic increase in oxytocin release and a decrease in parathyroid hormone–related peptide (PTHrP) expression. This phase also involves placental separation and continued uterine contractions.

Women undergo major endocrinologic and metabolic changes that establish, maintain, and end pregnancy. The aim of these changes is the safe delivery of an infant that can survive outside of the uterus. The maturation of the fetus and the adaptation of the mother are regulated by a variety of hormones and transmitters (Table 5-1). This chapter deals with the properties, functions, and interactions of the most important of these hormonal and nonhormonal substances as they relate to pregnancy and parturition.

TABLE 5-1

HORMONES AND TRANSMITTERS OF PREGNANCY AND PARTURITION

Hormone/Transmitter	Source	Function(s)	Clinical Comments
Human chorionic gonadotropin (hCG)	Placental trophoblastic tissue	Prevents regression of (rescues) the corpus luteum of pregnancy; increases T-cells that affect immunity	A likely regulator of a process that provides immune tolerance for the fetus; other trophic activities
Human placental lactogen (hPL)	Placenta	Antagonizes maternal glucose use so more is available for the fetus	Low values found in pregnancy loss; normal levels may increase risk of gestational diabetes
Corticotropin-releasing hormone (CRH)	Placenta	Stimulates fetal adrenocorticotropic hormone (ACTH) secretion, which allows the fetal adrenal to secrete DHEA-S for progesterone production; CRH may facilitate vasodilation	Fetal cortisol stimulates placental CRH release and fetal ACTH secretion; elevated levels may predict an increased risk of preterm birth
Prolactin	Maternal and fetal (late pregnancy) anterior pituitary glands	Stimulation of postpartum milk production	May play a role in fetal adrenal growth, as well as fluid and electrolyte membrane transfer
Progesterone (P4)	Placenta; precursors come from the maternal circulation	Prevents uterine contractions; suppresses gap junction formation	Maintains uterine quiescence
17-Hydroxyprogesterone (17-OHP)	Corpus luteum	Supports early pregnancy until placental production of P4 begins	Corpus luteum function is essential in early pregnancy
Estrogens Estriol (E3), estrone (E1), and estradiol (E2)	Placenta; conversion of androgens (DHEA, DHEA-S) from the fetal adrenal into estrogens	Estriol (E3) is the main estrogen of pregnancy; it increases uterine blood flow and prepares the breast for lactation	Placenta cannot convert progesterone to estrogen; lacks the enzyme 17α-hydroxylase; has role in lung surfactant production
Androgens Dehydroandrosterone (DHEA) and its sulfate (DHEA-S) Dihydrotestosterone (DHT)	During pregnancy, androgens originate mostly in the fetal adrenal cortex	DHEA production is favored, and is a precursor for placental estrogen production	Fetal testis produces testosterone, which is converted to DHT; this is needed for development of male external genitalia; hCG stimulates testosterone production
Cortisol	Derived from circulating cholesterol	Plays a major role in the activation of labor by increasing placental release of CRH and prostaglandins	Late in pregnancy, cortisol promotes the production of lung surfactant
Oxytocin	Maternal hypothalamus and posterior pituitary	Can cause uterine contractions; possible effects on emotion and well-being	Related to uterine contractions, but not the natural initiation of labor; facilitator of childbirth and breastfeeding
Relaxin	Corpus luteum and placenta	Primary function is to promote implantation; also causes uterine relaxation	Too much relaxin can result in a shortened cervix and increased risk of premature labor; too little can interfere with implantation
Prostaglandins PGE_2 $PGF_{2\alpha}$	Placental production from arachidonic acid	Thought to play a major role in the initiation of labor	Not true hormones; act at or close to the site of production; prostaglandin synthetase inhibitors can prolong labor
Leukotrienes	Placental production from arachidonic acid	Initiate changes in the endometrium that allow for implantation	Not true hormones; act at or close to the site of production
Parathyroid hormone–related peptide (PTHrP)	Uterus and other organs	Relaxes the uterus and allows for stretch without contractions	Allows for fetal growth during pregnancy; gene that activates PTHrP is off during parturition

Fetoplacental Unit

The concept of the fetoplacental unit is based on observations of the interactions between hormones of fetal, placental, and maternal origin. **The fetoplacental unit largely controls the endocrinologic events of the pregnancy.** Although the fetus, the placenta, and the mother all provide input, the fetus appears to play the most active and controlling role in its growth and maturation, and probably also in the events that lead to parturition.

FETUS

The adrenal gland is the major endocrine component of the fetus. In mid-pregnancy, it is larger than the fetal kidney. The fetal adrenal cortex consists of an outer definitive, or adult, zone and an inner, fetal, zone. The definitive zone later develops into the three components of the adult adrenal cortex: the zona fasciculata, the zona glomerulosa, and the zona reticularis. During fetal life, the definitive zone secretes primarily glucocorticoids and mineralocorticoids. **The fetal zone, at term, constitutes 80% of the fetal gland and primarily secretes androgens during fetal life.** It involutes following delivery and completely disappears by the end of the first year of life. The fetal adrenal medulla synthesizes and stores catecholamines, which play an important role in maintaining fetal homeostasis. The overall role of the fetal adrenal during fetal growth and maturation is not completely understood.

PLACENTA

The placenta, which functions as an "extra brain" during pregnancy, is unique because it contains genes from both the mother and father. In addition, it is the source of a brain peptide, corticotropin-releasing hormone (CRH), which has a very important regulatory role in pregnancy. Thus, the placenta produces both steroids and peptide hormones in amounts that vary with gestational age. Precursors for progesterone synthesis come from the maternal circulation. **Because of the lack of the enzyme 17α-hydroxylase, the human placenta cannot directly convert progesterone to estrogen** but must use androgens, largely from the fetal adrenal gland, as its source of precursor for estrogen production.

MOTHER

The mother adapts to pregnancy through major endocrinologic and metabolic changes. **The ovarian corpus luteum produces progesterone (mostly 17-hydroxyprogesterone) in early pregnancy** until its production shifts to the placenta. **The maternal hypothalamus and posterior pituitary produce and release oxytocin,** which causes uterine contractions and milk letdown. **The anterior pituitary produces prolactin,** which stimulates milk production. Several important changes in maternal metabolism are described later in the chapter.

Hormones

The fetoplacental unit produces a variety of hormones to support the maturation of the fetus and the adaptation of the mother.

PEPTIDE HORMONES

Human Chorionic Gonadotropin

Human chorionic gonadotropin (hCG) is secreted by trophoblastic cells of the placenta and maintains pregnancy. This hormone is a glycoprotein with a molecular weight of 40,000 to 45,000 and **consists of two subunits: alpha (α) and beta (β).** The α subunit is shared with luteinizing hormone (LH) and thyroid-stimulating hormone (TSH). **The specificity of hCG is related to its β subunit (β-hCG),** and a radioimmunoassay that is specific for the β subunit allows positive identification of hCG. Newer immunoassays for hCG are able to accurately measure low levels of hCG based on the entire molecule and not just the beta subunit. The presence of hCG at times other than pregnancy signals the presence of an hCG-producing tumor, usually a hydatidiform mole, choriocarcinoma, or embryonal carcinoma (a germ cell tumor).

During pregnancy, hCG begins to rise 8 days after ovulation (9 days after the midcycle LH peak). This provides the basis for virtually all immunologic or chemical pregnancy tests. With continuing pregnancy, hCG values peak at 60 to 90 days and then decline to a moderate, more constant level. **For the first 6 to 8 weeks of pregnancy, hCG maintains the corpus luteum and thereby ensures continued progesterone output until progesterone production shifts to the placenta.** Titers of hCG may be abnormally low in patients with an ectopic pregnancy or threatened abortion and abnormally high in those with trophoblastic disease (e.g., moles or choriocarcinoma). This hormone may also regulate steroid biosynthesis in the placenta and the fetal adrenal gland, and stimulate testosterone production in the fetal testicle. Early pregnancy is characterized by an increase in regulatory T cells (Tregs), which are known to facilitate maternal immune tolerance of the fetus. Recent animal research has shown that hCG acts as a central regulator of this immune tolerance during pregnancy.

Human Placental Lactogen

Human placental lactogen (hPL) originates in the placenta. It is a single-chain polypeptide with a molecular weight of 22,300, and it resembles pituitary growth hormone and human prolactin in structure. Maternal serum concentrations parallel placental weight, rising throughout gestation to maximum levels in the last 4 weeks. At term, hPL accounts for 10% of all placental protein production. Low values are found with threatened abortion and intrauterine fetal growth restriction. **Human placental lactogen antagonizes the cellular action of insulin and decreases maternal glucose utilization, which increases glucose availability to the fetus.** This may play a role in the pathogenesis of gestational diabetes.

Corticotropin-Releasing Hormone

During pregnancy the major source of CRH is the placenta and it can be measured as early as 12 weeks' gestation, when it passes into the fetal circulation. This 41-amino acid peptide stimulates fetal adrenocorticotropic hormone (ACTH) secretion, which in turn stimulates the fetal adrenal to secrete dehydroepiandrosterone sulfate (DHEA-S), an important precursor of estrogen production by the placenta. The fetal adrenal gland early in pregnancy does not have the enzymes to produce cortisol, but as gestational age increases, it becomes more capable. **Fetal cortisol stimulates placental CRH release, which then stimulates fetal ACTH secretion, completing a positive feedback loop that plays an important role in the activation and amplification of labor, both preterm and term.** Elevated levels of CRH in mid-gestation have been found to be associated with an increased risk of subsequent spontaneous preterm labor.

Prolactin

Prolactin is a peptide from the anterior pituitary with a molecular weight of about 20,000. Normal nonpregnant levels are approximately 10 ng/mL. **During pregnancy, maternal prolactin levels rise in response to increasing maternal estrogen output that stimulates the anterior pituitary lactotrophs. The main effect of prolactin is stimulation of postpartum milk production.** In the second half of pregnancy, prolactin secreted by the fetal pituitary may be an important stimulus of fetal adrenal growth. Prolactin may also play a role in fluid and electrolyte shifts across the fetal membranes.

STEROID HORMONES

Progesterone

Progesterone is the most important human progestogen. **In the luteal phase, it induces secretory changes in the endometrium and in pregnancy, higher levels induce decidual changes. Up to the sixth or seventh week of pregnancy, the major source of progesterone (as 17-hydroxyprogesterone) is the ovarian corpus luteum.** Thereafter, the placenta begins to play the major role. **If the corpus luteum of pregnancy is removed before 7 weeks and continuation of the pregnancy is desired, progesterone should be given to prevent spontaneous abortion.** Circulating progesterone is mostly bound to carrier proteins, and less than 10% is free and physiologically active.

The myometrium receives progesterone directly from the venous blood draining the placenta. **Progesterone prevents uterine contractions and may also be involved in establishing an immune tolerance for the products of conception.** Progesterone also suppresses gap junction formation, placental CRH expression, and the actions of estrogen, cytokines, and prostaglandin. This steroid hormone therefore plays a central role in maintaining uterine quiescence throughout most of pregnancy.

The fetus inactivates progesterone by transformation to corticosteroids or by hydroxylation or conjugation to inert excretory products. However, the placenta can convert these inert materials back to progesterone. Steroid biochemical pathways are shown in Figure 5-1.

Estrogens

Both fetus and placenta are involved in the biosynthesis of estrone, estradiol, and estriol. **Cholesterol is converted to pregnenolone in the placenta. This precursor is converted into DHEA-S largely in the fetal, and to a lesser extent the maternal, adrenals.** The DHEA-S is further metabolized by the placenta to estrone (E1) and, via testosterone, to estradiol (E2). **Estriol (E3), the most abundant estrogen in human pregnancy, is synthesized in the placenta from 16α-hydroxy-DHEA-S, which is produced in the fetal liver from adrenal DHEA-S.** Placental sulfatase is required to deconjugate 16α-hydroxy-DHEA-S before conversion to E3 (Figure 5-2). Steroid sulfatase activity in the placenta is high, except in rare cases of sulfatase deficiency.

Estrogens have essential roles during pregnancy and parturition. They increase uterine blood flow which allows for necessary uterine growth. They help to prepare the breast tissue for lactation and they stimulate the production of hormone-binding globulins in the liver. They also play a role, along with cortisol, in lung surfactant production.

A sudden decline of estriol in the maternal circulation may indicate fetal compromise in a neurologically intact fetus. Anencephalic fetuses lack a hypothalamus and have hypoplastic anterior pituitary and adrenal glands; thus, estriol production is only about 10% of normal.

Androgens

During pregnancy, androgens originate mainly in the fetal zone of the fetal adrenal cortex. Androgen secretion is stimulated by ACTH and hCG, the latter being effective primarily in the first half of pregnancy, when it is present in high concentration. The fetal adrenal favors production of DHEA over testosterone and androstenedione. **Fetal androgens enter the umbilical and placental circulation and serve as precursors for estrone, estradiol, and estriol** (see Figure 5-1).

The fetal testis also secretes androgens, particularly testosterone, which is converted within target cells to **dihydrotestosterone** (DHT), which is required for the

Reference

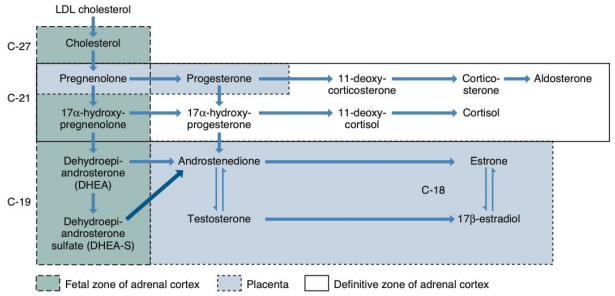


FIGURE 5-1 Main pathways of steroid hormone biosynthesis. Adrenal DHEA is largely transported as its sulfate, DHEA-S, which can also be formed from steroid sulfates starting with cholesterol sulfate. *LDL*, Low-density lipoprotein.

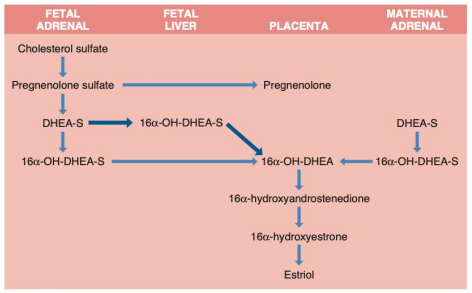


FIGURE 5-2 Formation of estriol in the fetal-placental unit. *DHEA-S*, Dehydroepiandrosterone sulfate.

development of male external genitalia. The main trophic stimulus appears to be hCG.

Glucocorticoids

Cortisol is derived from circulating cholesterol (see Figure 5-1). Maternal plasma cortisol concentrations rise throughout pregnancy and are the primary stimulus for CRH production by the placenta. The diurnal rhythm of cortisol secretion persists during pregnancy unless the patient has significant psychosocial stress, which elevates the morning and late afternoon cortisol level at which time the diurnal rhythm is lost. The plasma level of transcortin rises in pregnancy, probably stimulated by estrogen, and the plasma-free cortisol concentration doubles.

Both the fetal adrenal and the placenta participate in cortisol metabolism. The fetal adrenal is stimulated by ACTH, originating from the fetal pituitary, to produce both cortisol and DHEA-S. In contrast to DHEA-S, which is produced in the fetal zone, cortisol originates in the definitive zone (see Figure 5-1). Toward the end of pregnancy **cortisol promotes differentiation of type II alveolar cells and the biosynthesis and release of surfactant into the alveoli.** Surfactant decreases the force required to inflate the lungs. Insufficiency of surfactant leads to respiratory distress in the premature infant, which can cause death. **Cortisol also plays an important role in the activation of labor,** increasing the release of placental CRH and prostaglandins.

OTHER HORMONES AND TRANSMITTERS

Oxytocin

The oxytocic prohormone, which originates in the supraoptic and paraventricular nuclei of the maternal hypothalamus, migrates down the nerve fibers, and oxytocin accumulates at the nerve endings in the posterior pituitary. Oxytocin is a nonapeptide which is released from the posterior pituitary by various stimuli, such as distention of the birth canal and mammary stimulation. **Oxytocin causes uterine contractions, but impairment of oxytocin production, as in diabetes insipidus, does not interfere with normal labor.** Fluctuations in circulating oxytocin levels before the onset of labor do not correspond to changes in uterine activity. **Maternal serum oxytocin levels rise only during the first stage of labor.** Oxytocin can be administered to induce labor, especially in term pregnancies, or to increase the frequency and strength of contractions during spontaneous labor.

Recently, oxytocin has been shown to affect regions of the brain involved in emotional, cognitive, and social behaviors. The impact on "pro-social" behaviors includes positive effects on relaxation, trust, and psychological stability. If confirmed, these effects could help during labor, childbirth, and aftercare.

Relaxin

Relaxin is a peptide hormone that originates mostly from the ovarian corpus luteum. The placenta also produces relaxin and it reaches its peak concentration in the maternal circulation at the 10th week of pregnancy and then declines. **Relaxin is associated with the softening of the cervix,** which is one of the anatomical signs of pregnancy. **Its primary function appears to be in promoting implantation of the embryo by facilitating angiogenesis.** During hyperstimulation of the ovaries of women undergoing in vitro fertilization (IVF), the ovaries produce excessive levels of relaxin. This excess of relaxin has been shown to be associated with shortening of the cervix and an increased risk of preterm labor.

Prostaglandins and Leukotrienes

Prostaglandins are a family of ubiquitous, biologically active lipids that are involved in a broad range of physiologic and pathophysiologic responses. **They are not true hormones** in that they are not synthesized in one gland and transported via the circulating blood to a target organ. Rather, they are synthesized at or near their site of action. **Prostaglandin E_2 (PGE_2) and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), prostacyclin, and thromboxane A_2 are synthesized in the endometrium, myometrium, the fetal membranes, decidua, and placenta. PGE_2 and $PGF_{2\alpha}$ cause contraction of the uterus.** Their receptors in the myometrium are downregulated during pregnancy. Prostaglandins can also cause contraction of other smooth muscles, such as those of the intestinal tract. Hence, when used pharmacologically, prostaglandins may give rise to undesirable side effects such as nausea, vomiting, and diarrhea. The amniotic fluid concentrations of PGE_2 and $PGF_{2\alpha}$ rise throughout pregnancy and increase further during spontaneous labor. Levels are lower in women who require oxytocin for induction of labor than in women going into spontaneous labor. Administration of PGE_2 or $PGF_{2\alpha}$ by various routes induces labor or abortion at any stage of gestation. **Various synthetic prostaglandin derivatives are currently in use to terminate pregnancy at any stage and to induce labor at term.**

Prostaglandins are thought to play a major role in the initiation and control of labor. Prostaglandin synthesis begins with the formation of arachidonic acid, an obligatory precursor of the prostaglandins of the "2" series (i.e., PGE_2, $PGF_{2\alpha}$). Arachidonic acid is stored in esterified form as glycerophospholipid in the trophoblastic membranes. The initial step is the hydrolysis of glycerophospholipids, which is catalyzed by phospholipase A_2 or C. **Phospholipase A_2 preferentially acts on chorionic phosphatidyl ethanolamine to release arachidonic acid** (Figure 5-3). Free arachidonic acid does not accumulate. Labor appears to be accompanied by a cascade of events in the chorion, amnion, and decidua that release arachidonic acid from its stored form and convert it to active prostaglandins. 17β-Estradiol stimulates several enzymes active in the synthesis of prostaglandins from arachidonic acid.

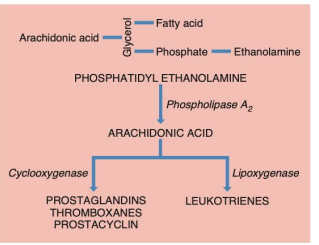


FIGURE 5-3 Diagram of prostaglandin and leukotriene biosynthesis.

There are two cyclooxygenase isoenzymes referred to as COX-1 or PGHS-1, and COX-2 or PGHS-2. These isoenzymes originate from separate genes. COX-1 is expressed in quiescent cells, whereas COX-2 is inducible. It is expressed at sites of inflammation upon cell activation, and potentiates the inflammatory process. **COX-1 mRNA expression is low in fetal membranes** and does not change with gestational age, whereas **COX 2 mRNA expression in the amnion increases with gestational age.**

Increased phospholipase A_2 activity may lead to premature labor. Endocervical, intrauterine, or urinary tract infections are often associated with premature labor. Many of the organisms producing these infections have phospholipase A_2 activity, which could produce free arachidonic acid, followed by prostaglandin synthesis, which could trigger labor.

Prostaglandin synthetase inhibitors can prolong gestation. Nonsteroidal antiinflammatory drugs (NSAIDs) inhibit phospholipase A_2, whereas aspirin-like drugs inhibit cyclooxygenase. Because PGE_2 keeps the ductus arteriosus open, premature closure of the ductus may occur after ingestion of NSAIDs or aspirin in large amounts or for a prolonged period of time, resulting in fetal pulmonary hypertension and death.

An additional pathway for arachidonic acid metabolism is the conversion of arachidonic acid to leukotrienes (see Figure 5-3). Both prostaglandins and leukotrienes induce decidualization, which means that they initiate changes in the endometrium during early pregnancy to facilitate implantation of the fertilized ovum.

Although $PGF_{2\alpha}$ is more potent in producing uterine contractile activity, **PGE_2 is the most potent prostaglandin for ripening the cervix** by inducing changes in the connective tissue. Hence, PGE_2 and its synthetic derivatives are clinically useful for cervical ripening before the induction of labor or abortion.

Changes in Maternal Metabolism

Maternal metabolism adapts to pregnancy through endocrinologic regulation as described below.

ANGIOTENSIN-ALDOSTERONE

Aldosterone is a mineralocorticoid synthesized in the zona glomerulosa of the adrenal cortex. The main source in pregnancy is the maternal adrenal. The fetal adrenal and the placenta do not participate significantly in aldosterone production, although the fetal adrenal is capable of synthesizing it. **Aldosterone secretion is regulated by the renin-angiotensin system.** Increased renin formed in the kidney converts angiotensinogen (renin-substrate) to angiotensin I, which is further metabolized to angiotensin II, which in turn stimulates aldosterone secretion. **Aldosterone stimulates the absorption of sodium and the secretion of potassium in the distal tubule of the kidney, thereby maintaining sodium and potassium balance.** The concentration of renin-substrate (a plasma protein), rises in pregnancy. It is thought that the high concentrations of progesterone and estrogen present during pregnancy stimulate renin and renin-substrate formation, thus giving rise to increased levels of angiotensin II and greater aldosterone production. **Aldosterone secretion rates decline in pregnancy-induced hypertension and, in some cases, may fall below nonpregnant levels.**

CALCIUM METABOLISM

Although calcium absorption is increased in pregnancy, total maternal serum calcium declines. The fall in total calcium parallels that of serum albumin, because approximately half of the total calcium is bound to albumin. **Ionic calcium, the physiologically important calcium fraction, remains essentially constant throughout pregnancy because of increased maternal production of parathyroid hormone. The latter facilitates the transfer of calcium across the placenta to the fetus for adequate bone development, and at the same time the mobilization of calcium from the mother's skeleton to maintain adequate calcium homeostasis.** In late pregnancy, coinciding with maximal calcification of the fetal skeleton, increased serum parathyroid hormone levels enhance both maternal intestinal absorption of calcium and bone resorption.

Calcium ions are actively transported across the placenta, and fetal serum levels of total as well as ionized calcium are higher than maternal levels in late pregnancy. High fetal ionic calcium suppresses fetal parathyroid hormone production and parathyroid hormone does not cross the placenta. Furthermore, calcitonin production is stimulated, thus providing the fetus with ample calcium for calcification of the skeleton. In the first 24 to 48 hours postpartum, the total serum calcium concentration in the neonate usually falls, while the phosphorus concentration rises. Both adjust to adult levels within 1 week.

Parturition

Parturition means childbirth, and labor is the physiologic process by which a fetus is expelled from the uterus to the outside world.

BIOCHEMICAL BASIS OF CONTRACTION

Muscle contraction is brought about by the sliding of actin and myosin filaments fueled by adenosine triphosphate (ATP) and calcium. **While skeletal muscle requires innervation, contraction of smooth muscles such as the myometrium is triggered primarily by hormonal stimuli.** Hormonal receptors have been found in the myometrial cell membrane.

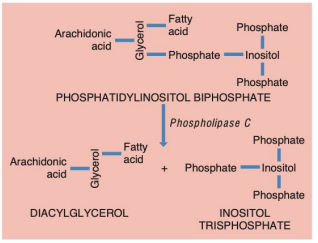


FIGURE 5-4 Diagram of inositol trisphosphate formation.

The binding of oxytocin and prostaglandins to their respective receptors activates phospholipase C, which hydrolyzes phosphatidylinositol bisphosphate, a lipid present in the cell membrane, to inositol trisphosphate and diacylglycerol (Figure 5-4). Inositol trisphosphate induces release of calcium from the sarcoplasmic reticulum, an intracellular calcium storage area. The resulting high intracellular free calcium concentration enables the myofibrils of the myometrium to contract. Subsequently, the calcium is pumped back into the sarcoplasmic reticulum with the help of ATP, and more calcium may enter from the extracellular fluid through both voltage-operated and receptor-operated channels that open briefly. **The maintenance of adequate maternal calcium levels is important because low maternal serum calcium levels have been observed in women at risk for cesarean delivery.**

Unlike the heart, in which the bundle of His is present, no anatomic structures for synchronization of contractions have been found in the uterus; however, recently it has been observed that vitamin D deficiency during pregnancy is associated with myometrial dysfunction and a greater risk of cesarean delivery. Uterine contractions spread as current flows from cell to cell through areas of low resistance. Such areas are associated with gap junctions, which become especially prominent at parturition. **Estradiol and prostaglandins promote the appearance of gap junctions,** whereas progesterone opposes this action of estradiol.

HORMONAL CONTROL OF GESTATIONAL LENGTH AND INITIATION OF LABOR

Gestational length is under the hormonal control of the fetus. Each species has not only a unique gestational length, but also unique mechanisms for controlling that length. Thus, although animal models provide important insights, they do not provide specific information concerning the control of the human gestational length or the mechanisms that control the initiation of labor.

Animal Models

Most studies have been conducted in sheep, where the fetus appears to control the onset of labor. The fetal hypothalamus stimulates the fetal pituitary to secrete ACTH, which brings about a surge of cortisol from the fetal adrenal. The cortisol surge induces the placental enzyme 17α-hydroxylase and the formation of androgens, which are precursors of estrogen (see Figure 5-1), while simultaneously decreasing progesterone formation. The rise in the estrogen-to-progesterone ratio leads to (1) greater secretion of prostaglandins; (2) formation of myometrial gap junctions, which provide areas of low resistance to current flow and increase coordinated uterine contractions; (3) cervical ripening; and (4) the onset of labor. Administered ACTH, glucocorticoids, or dexamethasone can also initiate parturition. Removal of the fetal pituitary or adrenal, both of which are required for the cortisol surge, will result in prolonged pregnancy.

In a breed of Guernsey cows with a genetic defect resulting in fetal pituitary and adrenal dysfunction, pregnancy is prolonged, and normal vaginal delivery does not occur. **In the rabbit, parturition directly follows a decline in progesterone production secondary to a decline in corpus luteum function.** Abortion can be prevented by administration of progesterone.

The Human

Based upon animal and human research, the process of normal spontaneous human parturition can be divided into four stages.

PHASE 0: QUIESCENCE. Throughout the majority of pregnancy, the uterus remains relatively quiescent. Myometrial activity is inhibited during pregnancy by various substances, but **progesterone appears to play a central role in maintaining uterine quiescence.** Recently, it has been shown that various organs such as the lung, heart, bladder, and uterus are modulated by parathyroid hormone–related peptide (PTHrP), which is produced in each of these organs. This peptide hormone is stimulated by stretch, and during pregnancy PTHrP relaxes the uterus to facilitate fetal growth. At delivery, the gene that regulates PTHrP is turned off, allowing the uterus to contract and to begin the involution process. This reduces the risk of postpartum hemorrhage. Rare uterine contractions that occur during the quiescent phase are of low frequency and amplitude and are poorly coordinated; these are commonly referred to as **Braxton-Hicks contractions** in women. The poor coordination of these contractions is primarily due to an absence of gap junctions in the pregnant myometrium.

Reference

PHASE 1: ACTIVATION. Normally, the signals for myometrial activation can come from uterine stretch as a result of fetal growth, or from activation of the fetal hypothalamic-pituitary-adrenal (HPA) axis as a result of fetal maturation. Uterine stretch has been shown in animal models to increase gap junctions and contraction-associated proteins in the myometrium. It is currently thought that once fetal maturity has been reached (as determined by as yet unknown mechanisms), the fetal hypothalamus increases CRH secretion, which in turn stimulates ACTH expression by the fetal pituitary and cortisol and androgen production by the fetal adrenals. Recent data from pregnant mice suggest that the fetus signals the initiation of labor by secreting a major lung surfactant protein, SP-A, into the amniotic fluid.

These data support a critical role for the fetal HPA axis in the initiation of parturition, because surfactant protein synthesis is stimulated by glucocorticoids. The role of PTHrP may also be important in lung development and the onset of parturition. **The concept of a role for the fetal lung in the initiation of parturition is particularly attractive because the fetal lung is the last major organ to mature.**

PHASE 2: STIMULATION. Phase 2 involves a progressive cascade of events leading to a common pathway of parturition, and involving uterine contractility, cervical ripening, and decidual/fetal membrane activation. **This cascade probably begins with placental production of CRH.** Placental CRH synthesis is stimulated by glucocorticoids, in contrast to the inhibitory effect of glucocorticoids on maternal hypothalamic CRH synthesis. Placental CRH enters into the fetal circulation and, in turn, promotes fetal cortisol and DHEA-S production. This positive feedback loop is progressively amplified, thereby driving the process forward from fetal HPA activation to parturition and the placental production of estrogens.

For most of pregnancy, uterine quiescence is maintained by the action of progesterone. At the end of pregnancy in most mammals, maternal progesterone levels fall and estrogen levels rise. In human and nonhuman primate pregnancies, the concentrations of progesterone and estrogens continue to rise throughout pregnancy until delivery of the placenta. A functional progesterone withdrawal may occur in women and nonhuman primates by alterations in progesterone receptor (PR) expression. **There are two progesterone receptors (PRA and PRB) in the human myometrium.** In contrast to PRB, which increases progesterone action, **PRA inhibits progesterone action. The ratio of PRA to PRB in the myometrium in labor is increased, which in effect results in a progesterone withdrawal.**

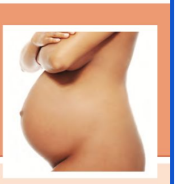
Functional progesterone withdrawal results in functional estrogen predominance, in part as a result of the increase in placental production of estrogen. The expression of estrogen receptor (ER) isoform, ERα, is normally suppressed by progesterone but as the expression of PR-A increases relative to that of PR-B, so does the expression of ERα in the laboring myometrium. The rising expression of ERα facilitates increased estrogen action. Increasing levels of estrogen also enhance expression of many estrogen-dependent contraction associated proteins (CAPs), including connexin 43 (gap junctions), oxytocin receptor, prostaglandin receptors, cyclooxygenase-2 (COX-2, which results in prostaglandin production), and myosin light-chain kinase (MLCK, which stimulates myometrial contractility and labor).

The progressive cascade of biological processes leads to a common pathway of parturition, involving cervical ripening, uterine contractility, and decidual/fetal membrane activation. **Cervical ripening is largely mediated by the actions of prostaglandins, uterine contractility by the actions of gap junctions and myosin light-chain kinase,** and **decidual/fetal membrane activation by the actions of enzymes such as metalloproteinases,** which ultimately lead to rupture of the membranes.

PHASE 3: INVOLUTION. During expulsion of the fetus, there is a dramatic increase in the release of maternal oxytocin which facilitates the initiation of the final phase of labor. It is thought that some of the increase in oxytocin comes from the fetal pituitary as a result of compression of the fetal head as it passes through the pelvis. Within a short time after the expulsion of the fetus from the uterus the effect of PTHrP decreases which facilitates the return of normal nonpregnant uterine contractility. This decrease accounts for the increased sensitivity of the uterus to oxytocin. **Phase 3 involves placental separation and continued uterine contractions.** Placental separation occurs by cleavage along the plane of the decidua basalis. Uterine contraction is essential to prevent bleeding from large venous sinuses that are exposed after delivery of the placenta, and is primarily effected by oxytocin. This is further supported by oxytocin let down during early breast feeding.

CHA

Maternal Physiologic and Immunologic Adaptation to Pregnancy



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CLINICAL KEYS FOR THIS CHAPTER

- The hemodynamic changes associated with pregnancy begin at 6 weeks' gestation and are associated with sodium and water retention. The mechanisms for these changes are secondary to elevations in the production of aldosterone, prostaglandins, atrial natriuretic peptide, and nitric oxide that reduce arterial vascular tone. This is followed by formation of arterial-venous shunts, due to invasion of the trophoblasts into the maternal spiral arteries. This invasion, completed at 22 weeks' gestation, allows maternal blood to flow easily into the intervillous placental space and to supply the fetus with adequate nutrition and with exchanges of oxygen and carbon dioxide.
- After complete invasion of the placenta into the spiral arteries, both the systolic and diastolic blood pressure fall (diastolic more than systolic). Toward the end of pregnancy, both diastolic and systolic pressures begin to increase. The gradual increase in the size of the fetus results in mechanical changes in the maternal circulatory and respiratory systems. For the respiratory system, the enlarging fetus and uterus increase the maternal minute ventilation needed to support the increase in oxygen consumption of the fetus and placenta. Maternal renal metabolic requirements are also increased.
- Renal changes during pregnancy play an important role in maintaining maternal-fetal homeostasis. The glomerular filtration rate (GFR) increases early in pregnancy and is maintained for the duration of the pregnancy. Renal function is important for the maintenance of intravascular volume, and the kidneys are able to decrease or increase sodium tubular reabsorption to maintain sodium balance.
- The placenta receives a significant amount of the cardiac output from the mother and the fetus returns at least 60% of its cardiac output to the placenta, suggesting that the placenta plays a vital role in the metabolic regulation of fetal homeostasis. The fetus has the advantage of having fetal hemoglobin that is capable of transferring greater amounts of oxygen than adult hemoglobin. The fetus, with a higher temperature and lower pH, can shift the oxygen-dissociation curve to the right, while the lower maternal temperature and higher maternal pH shifts the maternal curve to the left. This allows adequate oxygen transfer from the mother to the fetus and is referred to as the double Bohr effect.
- At no other time in the reproductive life of a woman is there an immune challenge as robust as the innate immune system in pregnancy. This system is an inflammatory response during early pregnancy followed by an adaptive immune response, T-lymphocyte helper cell-2 (Th-2), in mid-pregnancy that is designed to prevent rejection of the fetus. The mechanism by which tolerance occurs is complex, and depends upon an organized regulation between Th-1 and Th-2 immunity.

Maternal physiologic adjustments to pregnancy are designed to support the requirements of fetal homeostasis and growth, without unduly jeopardizing maternal well-being. This is accomplished by remodeling maternal cardiovascular, respiratory, renal, and endocrinologic systems to deliver energy and growth substrates to the fetus, while removing inappropriate heat and waste products.

The uterus appears to be a privileged immunologic sanctuary for the fetus and placenta during pregnancy. The pregnant mother's own immunologic defense system remains intact, while allowing an antigenically dissimilar fetus to grow and thrive. At the present time, it is not completely understood how this maternal-fetal immunologic compatibility is regulated.

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.

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.

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

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.

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.

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.

Respiratory System

The major respiratory changes in pregnancy involve three factors: the mechanical effects of the enlarging uterus, the increased total body oxygen consumption, and the respiratory stimulant effects of progesterone.

RESPIRATORY MECHANICS IN PREGNANCY

The changes in lung volume and capacities associated with pregnancy are detailed in Table 6-3. **The diaphragm at rest rises to a level of 4 cm above its usual resting position.** The chest enlarges in transverse diameter by about 2.1 cm. Simultaneously, the subcostal angle increases from an average of 68.5 degrees to 103.5 degrees during the latter part of gestation. The increase in uterine size cannot completely explain the changes in chest configuration, as these mechanical changes occur early in gestation.

As pregnancy progresses, the enlarging uterus elevates the resting position of the diaphragm. This

TABLE 6-3
LUNG VOLUMES AND CAPACITIES IN PREGNANCY

Test	Definition	Change in Pregnancy
Respiratory rate	Breaths/minute	No significant change
Tidal volume	The volume of air inspired and expired at each breath	Progressive rise throughout pregnancy of 0.1-0.2 L
Expiratory reserve volume	The maximum volume of air that can be additionally expired after a normal expiration	Lowered by about 15% (0.55 L in late pregnancy compared with 0.65 L postpartum)
Residual volume	The volume of air remaining in the lungs after a maximum expiration	Falls considerably (0.77 L in late pregnancy compared with 0.96 L postpartum)
Vital capacity	The maximum volume of air that can be forcibly inspired after a maximum expiration	Unchanged, except for possibly a small terminal diminution
Inspiratory capacity	The maximum volume of air that can be inspired from resting expiratory level	Increased by about 5%
Functional residual capacity	The volume of air in lungs at resting expiratory level	Lowered by about 18%
Minute ventilation	The volume of air inspired or expired in 1 min	Increased by about 40% as a result of the increased tidal volume and unchanged respiratory rate

Data from Main DM, Main EK: *Obstetrics and gynecology: a pocket reference,* Chicago, 1984, Year Book, p 14.

results in less negative intrathoracic pressure and a decreased resting lung volume, that is, a decrease in functional residual capacity (FRC). The enlarging uterus produces no impairment in diaphragmatic or thoracic muscle motion. Hence, **the vital capacity (VC) remains unchanged. These characteristics—reduced FRC with unimpaired VC—are analogous to those seen in a pneumoperitoneum** and contrast with those seen in severe obesity or abdominal binding, where the elevation of the diaphragm is accompanied by decreased excursion of the respiratory muscles. Reductions in both the expiratory reserve volume and the residual volume contribute to the reduced FRC.

OXYGEN CONSUMPTION AND VENTILATION

Total body oxygen consumption increases by about 15-20% in pregnancy. Approximately half of this increase is accounted for by the uterus and its contents, and the remainder is mainly related to increased maternal renal and cardiac work. Smaller increments are a result of greater breast tissue mass and increased work of the respiratory muscles.

In general, a rise in oxygen consumption is accompanied by cardiorespiratory responses that facilitate oxygen delivery (i.e., by increases in cardiac output and alveolar ventilation). To the extent that elevations in cardiac output and alveolar ventilation keep pace with the rise in oxygen consumption, the arteriovenous oxygen difference and the arterial partial pressure of carbon dioxide (P_{CO_2}), respectively, remain unchanged. **In pregnancy, the elevations in both cardiac output and alveolar ventilation are greater than those required to meet the increased oxygen consumption.** Hence, despite the rise in total body oxygen consumption, the arteriovenous oxygen difference and arterial P_{CO_2} both fall. The fall in P_{CO_2} (to 27-32 mm Hg), by definition, indicates hyperventilation.

The rise in minute ventilation reflects an approximately 40% increase in tidal volume at term; the respiratory rate does not change during pregnancy. During exercise, pregnant subjects show a 38% increase in minute ventilation and a 15% increase in oxygen consumption above comparable levels for postpartum subjects. The mechanism is thought to be secondary to the increase in minute ventilation secondary to increasing levels of progesterone and the increased metabolic rate of both the mother and her fetus(es).

When injected into normal nonpregnant subjects, **progesterone increases ventilation.** The central chemoreceptors become more sensitive to CO_2 (i.e., the curve describing the ventilatory response to increasing CO_2 levels has a steeper slope). **Such increased respiratory sensitivity to CO_2 is characteristic of pregnancy and probably accounts for the hyperventilation of pregnancy.**

In summary, both at rest and with exercise, minute ventilation and, to a lesser extent, oxygen consumption are increased during pregnancy. The respiratory stimulating effect of progesterone is probably responsible for the disproportionate increase in minute ventilation over oxygen consumption.

ALVEOLAR-ARTERIAL GRADIENT AND ARTERIAL BLOOD GAS MEASUREMENTS

The hyperventilation of pregnancy results in a respiratory alkalosis. Renal compensatory bicarbonate excretion leads to a final maternal blood pH of between 7.40 and 7.45. During labor (without conduction anesthesia), the hyperventilation associated with each contraction produces a further transient fall in P_{CO_2}. By the end of the first stage of labor, when cervical dilation is complete, a decrease in arterial P_{CO_2} persists, even between contractions.

In general, when alveolar P_{CO_2} falls during hyperventilation, alveolar partial pressure of oxygen (P_{O_2}) shows a corresponding rise, leading to a rise in arterial P_{O_2}. In the first trimester, the mean arterial P_{O_2} may be 106 to108 mm Hg. **There is a slight downward trend in arterial P_{O_2} as pregnancy progresses.** This reflects, at least in part, an increased alveolar-arterial gradient, possibly resulting from the decrease in functional residual capacity or FRC discussed previously, which leads to a ventilation-perfusion mismatch.

DYSPNEA OF PREGNANCY

In general, airway resistance is unchanged or even decreased in pregnancy. **Despite the absence of obstructive or restrictive effects, dyspnea is a common symptom in pregnancy. Some studies have suggested that dyspnea may be experienced by as many as 60-70% of women at some time during pregnancy.** Although the mechanism has not been established, the dyspnea of pregnancy may involve the increased sensitivity to the lower levels of P_{CO_2}.

Renal Physiology

ANATOMIC CHANGES IN THE URINARY TRACT

The urinary collecting system, including the calyces, renal pelves, and ureters, undergoes marked dilation in pregnancy, as is readily seen on intravenous urograms. It begins in the first trimester, is present in 90% of women at term, and may persist until the 12th to 16th postpartum week. Progesterone appears to produce smooth muscle relaxation in various organs, including the ureter. **As the uterus enlarges, partial obstruction of the ureter occurs at the pelvic brim in both the supine and the upright positions.** Because of the relatively greater effect on the right side, some have ascribed a role to the dilated ovarian venous plexus. Ovarian venous drainage is asymmetric, with the right vein emptying into the inferior vena cava and the left into the left renal vein.

RENAL BLOOD FLOW AND GLOMERULAR FILTRATION RATE

Renal plasma flow and the glomerular filtration rate (GFR) increase early in pregnancy. Maximum plateau elevations of at least 40-50% above nonpregnant levels are reached by mid-gestation, and they remain unchanged to term. As with cardiac output, renal blood flow and GFR (clinically measured as the creatinine clearance) reach their peak relatively early in pregnancy, before the greatest expansion in intravascular and extracellular volume occurs. **The elevated GFR is reflected in lower serum levels of creatinine and urea nitrogen,** as noted in Table 6-1.

Pregnancy is associated with large reductions in resistance in the afferent and efferent arterioles of the renal arteries, which appears to involve **vasorelaxation induced by relaxin, endothelin, and nitric oxide.** The resulting rise in renal plasma flow accounts for the hyperfiltration.

RENAL TUBULAR FUNCTION

Although 500 to 900 mEq of sodium is retained during pregnancy, **sodium balance is maintained with exquisite precision.** Despite the large amounts of sodium consumed daily (100 to 300 mEq), only 20 to 30 mEq of sodium is retained every week. Pregnant women, given high or low sodium diets, are able to decrease or increase their sodium tubular reabsorption, respectively, to maintain their sodium and fluid balance.

Pregnant women are also able to maintain their fluid balance with no change in the concentrating or diluting ability of the kidney. Plasma osmolarity is reduced by approximately 10 mOsm/kg of water. **Potassium metabolism during pregnancy remains unchanged,** although about 350 mEq of potassium is retained during pregnancy for fetoplacental development and expansion of maternal red cell mass.

The hyperventilation (low partial pressure of CO_2 in arterial blood [P_{aCO_2}]) of pregnancy results in respiratory alkalosis, which is compensated by renal excretion of bicarbonate. As a result, maternal renal buffering capacity is reduced.

FLUID VOLUMES

The maternal extracellular volume, which consists of intravascular and interstitial components, increases throughout pregnancy, leading to a state of physiologic extracellular hypervolemia. The intravascular volume, which consists of plasma and red cell components, increases approximately 50% during pregnancy. Maternal interstitial volume shows its greatest increase in the last trimester.

The magnitude of the rise in maternal plasma volume correlates with the size of the fetus; it is particularly marked in cases of multiple gestation. Multiparous women with poor reproductive histories show smaller increments in plasma volume and GFR when compared with those with a history of normal pregnancies and normal-sized babies.

RENIN-ANGIOTENSIN SYSTEM IN PREGNANCY

Plasma concentrations of renin, renin substrate, and angiotensin I and II are increased during pregnancy. **Renin levels remain elevated throughout pregnancy,** with at least a portion of the renin circulating in a high-molecular-weight form.

The uterus and placenta, like the kidney, **can produce renin,** and extremely high concentrations of renin occur in the amniotic fluid. The physiologic role of uterine renin has not been established. Recently, the renin-angiotensin system has been shown to participate in the regulation of maternal-placental-fetal blood flow that is altered by various disease states such as preeclampsia, obesity, and diabetes.

Homeostasis of Maternal Energy Substrates

The metabolic regulation of energy substrates, including glucose, amino acids, fatty acids, and ketone bodies, is complex and interrelated.

INSULIN EFFECTS AND GLUCOSE METABOLISM

In pregnancy, the insulin response to glucose stimulation is augmented. By the 10th week of normal pregnancy and continuing to term, fasting concentrations of insulin are elevated and those of glucose reduced. Until mid-gestation, these changes are accompanied by enhanced intravenous glucose tolerance (although oral glucose tolerance remains unchanged). **Glycogen synthesis and storage by the liver increases, and gluconeogenesis is inhibited.** Thus, during the first half of pregnancy, the anabolic actions of insulin are potentiated.

After early pregnancy, insulin resistance emerges, so glucose tolerance is impaired. The fall in serum glucose for a given dose of insulin is reduced compared with the response in earlier pregnancy. Elevation of circulating glucose is prolonged after meals, although fasting glucose remains reduced, as in early pregnancy.

A variety of humoral factors derived from the placenta have been suggested to account for the antiinsulin environment of the latter part of pregnancy. Perhaps the most important are cytokines and human placental lactogen (hPL), which antagonizes the peripheral effects of insulin. An increase in levels of free cortisol and other hormones may also be involved in the insulin resistance of pregnancy.

LIPID METABOLISM

The potentiated anabolic effects of insulin that characterize early pregnancy lead to the inhibition of lipolysis. **During the second half of pregnancy, probably as a result of rising hPL levels, lipolysis is augmented, and fasting plasma concentrations of free fatty acids are elevated.** Teleologically, the free fatty acids act as substrates for maternal energy metabolism, whereas glucose and amino acids cross the placenta to the fetus. In the humoral milieu of the second half of the pregnancy, the increased free fatty acids lead to ketone body formation (β-hydroxybutyrate and acetoacetate). **Pregnancy is thus associated with an increased risk of ketoacidosis, especially after prolonged fasting.**

In the context of maternal lipid metabolism, the most dramatic lipid change in pregnancy is the rise in fasting triglyceride concentration.

Placental Transfer of Nutrients

The transfer of substances across the placenta occurs by several mechanisms, including simple diffusion, facilitated diffusion, and active transport. **Low molecular size and lipid solubility promote simple diffusion.** Substances with molecular weights greater than 1000 Daltons, such as polypeptides and proteins, cross the placenta slowly, if at all.

Amino acids are actively transported across the placenta, making fetal levels higher than maternal levels. Glucose is transported by facilitated diffusion, leading to rapid equilibrium with only a small maternal-fetal gradient. **Glucose is the main energy substrate of the fetus,** although amino acids and lactate may contribute up to 25% of fetal oxygen consumption. The degree and mechanism of placental transfer of these and other substances are summarized in Table 6-4.

Other Endocrine Changes

THYROID

The thyroid gland undergoes moderate enlargement during pregnancy. This is not because of elevation of thyroid-stimulating hormone (TSH), which remains unchanged. Placenta-derived human chorionic gonadotropin (hCG) has a TSH-effect on the thyroid gland, which can result in abnormally low levels of TSH in the first trimester, when hCG concentrations are highest.

Circulating thyroid hormone exists in two primary active forms: thyroxine (T_4) and triiodothyronine (T_3). The former circulates in higher concentrations, is more highly protein-bound, and is less metabolically potent than T_3, for which it may serve as a prohormone. Circulating T_4 is bound to carrier proteins, approximately 85% to thyroxine-binding globulin (TBG) and most of the remainder to another protein, thyroxine-binding prealbumin. It is believed that only the unbound fraction of the circulating hormone is biologically active. **TBG is increased during pregnancy because the high estrogen levels induce increased hepatic synthesis.** The body responds by raising total circulating levels of T_4 and T_3 and the net effect is that **the free, biologically active concentration of each hormone is unchanged.** Therefore, clinically, the free T_4 index, which corrects the total circulating T_4 for the amount of binding protein, is an appropriate measure of thyroid function, with the same normal range as in the nonpregnant state.

Only minimal amounts of thyroid hormone cross the placenta. The small amount of thyroid hormone

Reference

TABLE 6-4

MATERNAL-FETAL TRANSFER DURING PREGNANCY

Function	Substance	Placental Transfer
Glucose homeostasis	Glucose	Excellent—"facilitated diffusion"
	Amino acids	Excellent—active transport
	Free fatty acids	Very limited—essential free fatty acids only
	Ketones	Excellent—diffusion
	Insulin	No transfer
	Glucagon	No transfer
Thyroid function	Thyroxine	Very poor—diffusion
	Triiodothyronine	Poor—diffusion
	Thyrotropin-releasing hormone	Good
	Thyroid-stimulating immunoglobulin	Good
	Thyroid-stimulating hormone	Negligible transfer
	Propylthiouracil	Excellent
Adrenal hormones	Cortisol	Excellent transfer and active placental conversion of cortisol to cortisone beginning at mid-pregnancy*
	Adrenocorticotropic hormone	No transfer
Parathyroid function	Calcium	Active transfer against gradient
	Magnesium	Active transfer against gradient
	Phosphorus	Active transfer against gradient
	Parathyroid hormone	Not transferred
Immunoglobulins	IgA	Minimal passive transfer
	IgG	Good—both passive and active transport from 7 wk gestation
	IgM	No transfer

Data from Main DM, Main EK: *Obstetrics and gynecology: a pocket reference,* Chicago, 1984, Year Book, p 37.
*At mid-gestation, placental 11β-hydroxysteroid dehydrogenase converts cortisol to cortisone.

that crosses the placenta is converted to reverse T_3 (rT_3) which is metabolically inactive. The fetus does not require thyroid hormone from the mother; it synthesizes thyroid hormone from its own thyroid gland to meet its requirements. The fetus does not require thyroid hormone for thermogenesis in utero and at birth it releases TSH in large amounts to begin the release of thyroid hormones for the purpose of thermogenesis.

ADRENAL

Adrenocorticotropic hormone (ACTH) and plasma cortisol levels are both elevated from 3 months' gestation to delivery. Circulating cortisol is also primarily bound to a specific plasma protein, corticosteroid-binding globulin (CBG) or transcortin. **Unlike the level of thyroid hormones, the mean unbound level of cortisol is elevated in pregnancy;** there is also some loss of the diurnal variation that characterizes its concentration in nonpregnant women.

Weight Gain in Pregnancy

The average weight gain in pregnancy uncomplicated by generalized edema is 12.5 kg (28 lb). The components of this weight gain are indicated in Table 6-5. The products of conception constitute only about 40% of the total maternal weight gain.

TABLE 6-5

ANALYSIS OF WEIGHT GAIN IN PREGNANCY

	Increase in Weight (Grams) Up To:			
Tissues and Fluids	10 wk	20 wk	30 wk	40 wk
Fetus	5	300	1500	3400
Placenta	20	170	430	650
Amniotic fluid	30	350	750	800
Uterus	140	320	600	970
Mammary gland	45	180	360	405
Blood	100	600	1300	1250
Interstitial fluid (no edema or leg edema)	0	30	80	1680
Maternal stores	310	2050	3480	3345
Total weight gained	650	4000	8500	12,500

Data from Hytten F, Chamberlain G, editors: *Clinical physiology in obstetrics,* Oxford, 1980, Blackwell Scientific, p 221.

Placental Transfer of Oxygen and Carbon Dioxide

FETAL OXYGENATION

The placenta receives 60% of the combined ventricular output, whereas the postnatal lung receives 100% of the cardiac output. Unlike the lung, which consumes little of the oxygen it transfers, **a significant percentage of the oxygen derived from maternal blood at term is consumed by placental tissue.** The degree of functional shunting of placental blood past exchange sites is approximately tenfold greater than in the lung. A major cause of this functional shunting is probably a mismatch between maternal and fetal blood flow at the exchange sites, analogous to the ventilation-perfusion inequalities that occur in the lung.

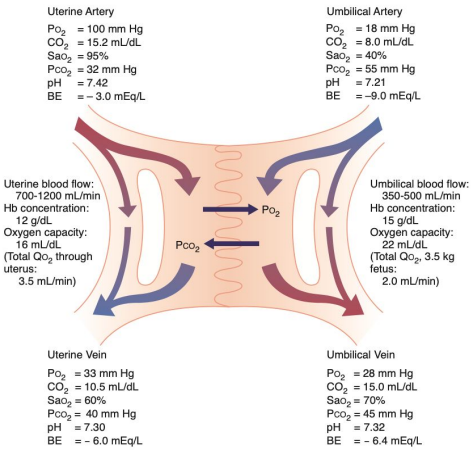

FIGURE 6-1 Placental transfer of oxygen and carbon dioxide. *BE,* Base excess; *Hb,* hemoglobin. (Adapted from Bonica JJ: *Obstetric analgesia and anesthesia,* ed 2, Amsterdam, 1980, World Federation of Societies of Anesthesiologists, p 29.)

The uteroplacental circulation subserves fetal gas exchange. Oxygen, carbon dioxide, and inert gases cross the placenta by simple diffusion. The rate of transfer is proportional to the difference in gas tension across the placenta and the surface area of the placenta, and the transfer rate is inversely proportional to diffusion distance between maternal and fetal blood. **The placenta normally does not pose a significant barrier to respiratory gas exchange, unless it becomes separated (abruption placenta) or edematous (severe hydrops fetalis).**

The anatomical distribution of uterine and umbilical blood flow and O_2 transfer across the placenta is depicted in Figure 6-1. A **maternal shunt,** which describes the fraction of blood shunted to the myoendometrium and is estimated to constitute 20% of uterine blood flow, is depicted. Similarly, a **fetal shunt,** which supplies blood to the placenta and fetal membranes and accounts for 19% of umbilical blood flow, is shown. The **maternal-to-fetal** Po_2 and Pco_2 gradients are calculated from measurements of gas tensions in the uterine and umbilical arteries and veins. **The umbilical vein of the fetus, like the pulmonary vein of the adult, carries the circulation's most highly oxygenated blood.** The umbilical venous Po_2 of about 28 mm Hg is relatively low by adult standards. This relatively low fetal tension is essential for survival in utero, because a high Po_2 initiates physiologic adjustments (e.g., closure of the ductus arteriosus and vasodilation of the pulmonary vessels) that normally occur in the neonate but would be harmful in utero.

Although not involved in respiratory gas exchange, fetal breathing movements are critically involved in lung development and in the development of respiratory regulation. Fetal breathing differs from that in the adult in that it is episodic, sensitive to fetal glucose concentrations, and inhibited by hypoxia. Because of its sensitivity to acute O_2 deprivation, fetal breathing is used clinically as an indicator of the adequacy of fetal oxygenation.

FETAL AND MATERNAL HEMOGLOBIN DISSOCIATION CURVES

Most of the oxygen in blood is carried by hemoglobin in red blood cells. The maximum amount of oxygen carried per gram of hemoglobin, that is, the amount carried at 100% saturation, is fixed at 1.37 mL. The hemoglobin flow rates depend on blood flow rates and hemoglobin concentration. The uterine blood flow at term has been estimated at 700 to 1200 mL/min, with about 75-88% of this entering the intervillous space. The umbilical blood flow has been estimated at 350 to 500 mL/min, with more than 50% going to the placenta (see Figure 6-1).

The hemoglobin concentration of the blood determines its oxygen-carrying capacity, which is expressed in milliliters of oxygen per 100 mL of blood. In the fetus at or near term, the hemoglobin concentration is about 18 g/dL and oxygen-carrying capacity is 20 to 22 mL/dL. The **maternal oxygen-carrying capacity of blood, which is generally proportional to the hemoglobin concentration, is lower than that of the fetus.**

The affinity of hemoglobin for oxygen, which is reflected as the percentage saturation at a given oxygen tension, depends on chemical conditions. As is illustrated in Figure 6-2, **when compared with that in nonpregnant adults, the binding of oxygen by hemoglobin is much greater in the fetus under standard conditions of Pco_2, pH, and temperature.** In contrast, maternal affinity is lower under these conditions, with 50% of hemoglobin saturated with O_2 at a Po_2 of 26.5 mm Hg (P_{50}) for mother compared with 20 mm Hg for the fetus.

In vivo, the greater fetal temperature and lower pH shift the O_2-dissociation curve to the right, while the lower maternal temperature and higher pH shift the maternal curve to the left. As a result, the O_2-dissociation curves for the fetal and maternal blood are not too dissimilar at the site of placental transfer. Maternal venous blood probably has an O_2-saturation of about 73% and a Po_2 of about 36 mm Hg, and the corresponding values for blood in the umbilical vein are about 63% and 28 mm Hg, respectively. **As the only source of O_2 for the fetus, blood in the umbilical vein has a higher O_2 saturation and Po_2 than blood in the fetal circulation** (Figure 6-3). In the presence of a low fetal arterial Po_2, fetal oxygenation is maintained by a high rate of blood flow to fetal tissues, which is supported by a very high cardiac output. This feature, along with the lower P_{50} of fetal blood, results in normal O_2 delivery to fetal organs.

The decrease in the affinity of hemoglobin for oxygen produced by a fall in pH is referred to as the Bohr effect. Because of the unique situation in the placenta, a double Bohr effect facilitates oxygen transfer from mother to fetus. When CO_2 and fixed acids are transferred from fetus to mother, the associated rise in fetal pH increases the fetal red blood cells' affinity for oxygen uptake. The concomitant reduction in maternal blood pH decreases oxygen affinity and promotes its unloading of oxygen from maternal red cells.

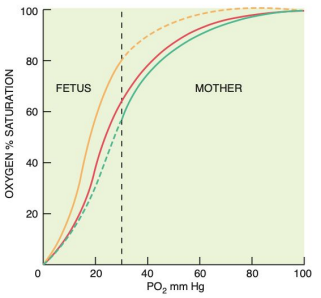

FIGURE 6-2 The oxygen dissociation curve for fetal blood compared with maternal blood. The central continuous curve is for normal adult blood under standard conditions. A vertical line at an oxygen partial pressure of 30 mm Hg divides the curves. The fetal curve normally operates below that level and the maternal curve above it. (Adapted from Hytten F, Chamberlain G, editors: *Clinical physiology in obstetrics,* ed 2, Oxford, 1991, Blackwell, p 418.)

Fetal Circulation

Several anatomic and physiologic factors must be noted in considering the fetal circulation (Table 6-6 and Figure 6-3).

The normal adult circulation is a series circuit with blood flowing through the right heart, the lungs, the left heart, the systemic circulation, and finally the right heart. In the fetus, the circulation is a parallel system with the cardiac outputs from the right and left ventricles directed primarily to different vascular beds. For example, the right ventricle, which contributes about 65% of the combined output, pumps blood primarily through the pulmonary artery, ductus arteriosus, and descending aorta. Only a small fraction of right ventricular output flows through the pulmonary circulation. The left ventricle supplies blood mainly to the tissues supplied by the aortic arch, such as the brain. **The fetal circulation is a parallel circuit characterized by channels (ductus venosus, foramen ovale, and**

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