Chapter 1

Anatomical and Physiological Changes in Pregnancy

Impact on Emergency Care

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Key Facts

Pregnancy is associated with profound anatomical, physiological, biochemical and endocrine changes that affect multiple organs and systems. These changes are essential to help the woman to adapt to the pregnant state and to aid fetal growth and survival. However, such anatomical and physiological changes may cause confusion during clinical examination of a pregnant woman. Similarly, changes in blood biochemistry during pregnancy may create difficulties in interpretation of results.

Conversely, clinicians also need to recognise pathological deviations in these normal anatomical and physiological changes during pregnancy to institute appropriate action to improve maternal and fetal outcomes.

Haematology

Blood Volume

There is an overall increase in plasma, red blood cells (RBCs) and total blood volume. Plasma volume increases by 15% during the first trimester; accelerates in the second trimester; peaks at around 32 weeks, reaching up to 50% above non-pregnant levels; and stays elevated until term. It returns to non-pregnant levels by 6 days post-delivery. There is often a sharp rise of up to 1 litre in plasma volume within the maternal circulation at 24 hours after delivery.

Red Blood Cell Volume

RBC volume falls during the first 8 weeks of pregnancy, increasing back to non-pregnant levels by 16 weeks and then rising to 30% above non-pregnant levels by term. The relatively smaller increase in RBC compared with plasma results in haemodilution and 'physiological anaemia' of pregnancy.

Coagulation and Fibrinolysis in Pregnancy

Plasma levels of factors VII, VIII, IX and XII, together with fibrinogen and fibrin degradation products, increase during pregnancy (fibrinogen from 2.5 to 4 g/L). Levels of factors XI and III decrease. These changes overall increase coagulability and make pregnancy a 'hypercoagulable' state.

Platelets

Pregnancy is associated with enhanced platelet turnover. Thrombocytopenia(platelets $< 100 \times 10^9$/L) occurs in 0.8%–0.9% of normal pregnant women, while increases in platelet factor and β-thromboglobulin suggest elevated platelet activation and consumption. Since there is no change in platelet count in the majority of pregnant women, there is probably an increase in platelet production to compensate for the increased consumption.

Cardiovascular System

Heart

The heart is pushed upwards and rotated forwards, with lateral displacement of the left border. All heart sounds are louder and the first sound is split. A systolic ejection murmur is normal and is due to turbulence secondary to increased blood flow through normal heart valves. A diastolic murmur is heard occasionally. Cardiac output is increased as a result of increased heart rate, reduced systemic vascular resistance and increased stroke volume. Heart rate is increased above non-pregnant values by 15% at the end of the first trimester. This increases to 25% by the end of the second trimester, but there is no further change in the third trimester.

Stroke volume is increased by about 20% at 8 weeks and up to 30% by the end of the second trimester, and then remains level until term.

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Blood Pressure

Systolic blood pressure does not show a significant drop in pregnancy. It may drop slightly, by 6%–8%. However, there is a marked drop in diastolic pressure. It is reduced in the first two trimesters by up to 20%–25% and returns to the non-pregnant level at term. This is due to the placenta acting as an arteriovenous shunt, together with peripheral vasodilating factors such as oestrogen, progesterone and increased endothelial synthesis of prostaglandin E2 and prostacyclins. Both blood pressure and cardiac output are reduced during epidural analgesia. In a supine position, 70% of mothers have a fall in blood pressure of at least 10%, and 8% have decreases of between 30% and 50%.

ECG Changes During Pregnancy

The following changes are of no clinical significance:

- Sinus tachycardia and atrial and ventricular ectopics. Rotation of the electrical axis of the heart to the left
- ST segment depression and T-wave inversion in inferior and lateral leads

Changes in echocardiograph during pregnancy:

- Left ventricular hypertrophy by 12 weeks
- 50% increase in left ventricular mass at term
- 12%–14% increase in aortic, pulmonary and mitral valve sizes

Respiratory System

Anatomical Changes

Capillary engorgement of the nasal and pharyngeal mucosa and larynx begins early in the first trimester. This may explain why many pregnant women complain of difficulty in nasal breathing, experience more episodes of epistaxis and experience voice changes. The thoracic cage increases in circumference by 5–7 cm because of the increase in both the anteroposterior and transverse diameters from flaring of the ribs. The level of the diaphragm rises by about 4 cm early in pregnancy even before it is under pressure from the enlarging uterus. This would account for the decrease in residual volume, since the lungs would be relatively compressed at forced expiration.

Physiology

During pregnancy minute ventilation increases by about 40%, from 7.5 to 10.5 L/minute and oxygen consumption increases by about 18%, from 250 to 300 mL/minute. Tidal volume increases gradually from the first trimester by up to 45% at term. Functional residual capacity is decreased by 20%–30% at term due to reductions of 25% in expiratory reserve volume and 15% in residual volume.

Table 1.1 Normal arterial blood gas values in pregnancy

pH	7.40–7.45
$PaCO_2$	3.7–4.2 kPa
PaO_2	13.0–14.0 kPa
HCO_3^-	18–21 mmol/L

Blood Gases

$PaCO_2$ decreases to 3.7–4.2 kPa by the end of the first trimester and remains at this level until term. Metabolic compensation for the respiratory alkalosis reduces the serum bicarbonate concentration to about 18–21 mmol/L, the base excess by 2–3 mmol/L and the total buffer base by about 5 mmol/L. PaO_2 in upright pregnant women is in the region of 14.0 kPa, higher than that in non-pregnant women. This is due to lower $PaCO_2$ levels, a reduced arteriovenous oxygen difference and a reduction in physiological shunt. Pregnant women maintain a normal arterial pH of 7.4–7.45 (Table 1.1).

Renal System

Kidney size increases by about 1 cm in length. There is marked dilatation of renal calyces, pelvis and ureters. Increase in glomerular filtration rate (GFR) by about 50% reaches a maximum at the end of the first trimester and is maintained at this augmented level until at least the 36th gestational week. The 24-hour creatinine clearance increases by 25% at 4 weeks after the last menstrual period and by 45% at 9 weeks. During the third trimester a consistent and significant decrease towards non-pregnant values occurs preceding delivery.

Gastrointestinal System

Gums may swell and bleed easily. The incidence of caries is increased. Barrier pressure (lower oesophageal sphincter [LOS] pressure minus gastric pressure) is reduced significantly during pregnancy compared with the non-pregnant state, due to increased intragastric pressure and reduced LOS pressure. LOS pressure appears to return to normal by 48 hours post-delivery.

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Endocrine System

Glucose Metabolism

Pregnancy is associated with an insulin-resistant condition, similar to that of type 2 diabetes. Early in pregnancy, increasing oestrogen and progesterone levels, which lead to pancreatic β-cell hypertrophy and insulin excretion, alter maternal carbohydrate metabolism. Secretion of other hormones such as human placental lactogen, prolactin, cortisol, oestrogen and progesterone induce insulin resistance. These hormones are found to be in significantly greater levels in pregnant women.

Thyroid Gland

There is increased synthesis of thyroxine-binding globulin (TBG) by the liver in pregnancy. This increase leads to a compensatory rise in serum concentrations of total thyroxine (T4) and triiodothyronine (T3). There is, however, no change in the amount of free circulating thyroid hormones. There is iodine deficiency as a result of loss through increased glomerular filtration and decreased renal tubular absorption. Active transport of iodine to the fetoplacental unit and fetal thyroid activity also deplete the maternal iodide pool further from the second trimester.

Pituitary Gland

There is significant enlargement of the pituitary gland during pregnancy. The growth is a result of an increase in the number of prolactin-secreting cells, with the proportion of lactotrophs increasing from 1% to 40%. This results in elevated prolactin levels to up to 10–20 times those of normal, non-pregnant values. These return to normal by 2 weeks postpartum, unless the woman breastfeeds. Gonadotropin levels are suppressed by the high concentrations of oestrogen and progesterone and are undetectable during pregnancy. Levels of basal growth hormone and antidiuretic hormone remain unchanged during pregnancy.

Adrenal Gland

Plasma corticosteroid binding globulin (CBG) concentrations increase during pregnancy. Levels of both free and bound cortisol also increase and levels of serum and urinary free cortisol increase three-fold by term. Adrenocorticotropic hormone (ACTH), which influences steroid secretion from adrenal cortex, remains within the normal range for non-pregnant women.

Skin

During pregnancy the skin undergoes a number of changes, mainly thought to be due to hormonal changes.

Hyperpigmentation: This occurs in up to 90% of women during pregnancy. This begins in the first trimester and is prominently noticed in areas of normal hyperpigmentation such as nipples, areola, perineum and vulva. Both oestrogens and progesterone, which have melanogenic stimulant properties, are thought to be responsible for this hyperpigmentation.

Linea nigra: This appears as an area of pigmentation extending from the symphysis pubis to xiphisternum. Although the pigmentation fades after delivery it rarely returns to pre-pregnancy levels.

Melasma: Develops in up to 70% of women, mainly in the second half of pregnancy. It appears as patches of light-brown facial pigmentation usually over the forehead, cheeks, upper lip, nose and chin.

Spider naevi: These present as a central red spot and reddish extensions which radiate outwards like a spider's web and occur on the face, the trunk and arms. Most appear in early pregnancy and regress following delivery, although in up to 25% of women they may persist. Recurrences are known to occur at the same site in subsequent pregnancies.

Striae gravidarum: These appear perpendicular to skin tension lines as pink linear wrinkles. They fade and become white and atrophic, although never disappear completely.

Palmar erythema: Palmar erythema is reddening of the palms at the thenar and hypothenar eminences. This is thought to be due to high levels of oestrogen in pregnancy and is seen in up to 70% of women by the third trimester and fades within 1 week of delivery.

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Table 1.2 Pregnancy-specific ranges for serum biochemistry

Biochemistry	Pregnancy-specific ranges
Full blood count	
Hb	10.5–14.0 g/dL
White blood cell count	5–11.0 g/dL
Platelets	100–450 × 10^9/L
Liver function	
Alkaline phosphatase	<500 IU/L
Alanine transaminase	<30 IU/L
Aspartate transaminase	<35 IU/L
Albumin	28–37 g/L
Bilirubin	3–14 µmol/L
Renal function	
Urea	2.8–3.8 mmol/L
Creatinine	50–80 µmol/L
Uric acid	0.14–0.2/0.35 µmol/L
Na	135–145 mmol/L
K	3.5–4.5 mmol/L
Protein excretion	<0.3/24 hours
Thyroid function	
Free T4	11–22 pmol/L
Free T3	43–45 pmol/L
TSH	0–4 mu/L

Hb, haemoglobin; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone.

Key Changes in Pregnancy

Normal anatomical, physiological and biochemical changes and their key implications during pregnancy are given in Tables 1.2, 1.3 and 1.4.

Optimising Clinical Practice

Liver and Gallbladder

Changes in bile acid composition can influence the likelihood of the occurrence of cholelithiasis. An increase in the bile acid pool, a decreased proportion of chenodeoxycholic acid and an increased proportion of cholic acid are findings that cause increased lithogenicity of bile in pregnancy. Decreases in gallbladder emptying can also promote biliary stasis and thus predispose pregnant women to biliary disease.

Endocrine System

Physiological changes (see 'Thyroid Gland' result in increased uptake of iodine from blood three-fold by the thyroid gland. In women with dietary insufficiency of iodine, the thyroid gland hypertrophies in order to trap a sufficient amount of iodine, which can result in enlargement and the appearance of goitre. Biochemical assessment of thyroid function in pregnancy should include assays of free T4 and in some cases, free T3. Management decisions should be principally based on these levels. Immunoradiometric assays of TSH are useful but should not be used in isolation because of the variable effects of gestation. As there is more conversion of T4 to T3, low levels of T4 are not necessarily indicative of hypothyroidism.

Haemorrhage

Due to the increase in circulating blood volume, compared with that in a non-pregnant woman, a pregnant woman could lose up to 1200–1500 mL of blood (35% of blood volume) before showing signs of shock. There could be a significant delay in the development of symptoms and signs of hypovolaemia in a pregnant woman. Therefore, efforts should be made to estimate postpartum blood loss and prompt treatment instituted to avoid the consequences of massive postpartum haemorrhage.

Asthma

Decreasing or stopping inhaled anti-asthmatic therapy during pregnancy is a frequent cause of potentially dangerous deterioration in disease control. Poorly controlled severe asthma presents more of a risk to the pregnancy than the medication used to prevent or treat it.

Epilepsy

The additional demand for folate during pregnancy leads to a rapid fall in red cell folate and to a high incidence of megaloblastic anaemia in women taking anticonvulsant drugs for control of epilepsy. Folate supplements should be given to all epileptic women taking anticonvulsants in pregnancy as well as before conception.

Constipation

Sluggish bowel movement during pregnancy can lead to severe or chronic abdominal pain. The presentation is widely varied. The most common is a dull, constant

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Table 1.3 Anatomical and physiological changes during pregnancy

Parameters		< 12 weeks	13–28 weeks	29 weeks
Haematological parameters	Plasma volume	↑10%–15%	Further rise (gradual)	↑ 50%
	Red cell volume	Falls	Reaches 'non-pregnant' levels	↑ 30%
	Total blood volume	↑ 10%	↑ 30%	↑ 45%
	Platelet count	→/↓	→ /↓	↓ 0–5%
	Haemoglobin	↓	↓	↓ 15%
	WBC/ESR			↑
	Factors V, VII, VIII, IX, XII, fibrinogen, vWF	→/↑	→ /↑	↑
	Prothrombin III, protein C, protein S, plasminogen activator inhibitor	→/↑	→ /↑	↓
		→/↓	→ /↓	
Cardiovascular physiology	Heart rate	↑ 15%	↑30%	↑30%
	Stroke volume	↑ 20%	↑30%	↑30%
	Cardiac output	↑ 30%–40%	↑30%–50%	Remains >50%
	Systolic and diastolic blood pressure	↓	→/↓	Non-pregnant value
Respiratory changes	Tidal volume	↑	↑	↑ 45
	FRC			↓ 20%–30%
	IRV			↑ 5%
	ERV			↓ 25%
	TLC			↓ 0–5%
Renal system	GFR	↑ 50%		Declines gradually
	Creatinine clearance	↑ 45%		Steady↓ towards non-pregnant values
	Glycosuria			↑
	Proteinuria			↑
Gastrointestinal	LOS pressure	↓	↓	↓
	Gastric acid secretion			↓
	Gastric emptying			↓
	Heartburn			↑

ERV, expiratory reserve volume; ESR, erythrocyte sedimentation rate; FRC, functional residual capacity; GFR, glomerular filtration rate; IRV, inspiratory reserve volume; LOS, lower oesophageal sphincter; TLC, total lung capacity; WBC, white blood cell count.

and sometimes colicky pain in the iliac fossae (the left more than the right). Care should be taken in prescribing laxatives, as medications resulting in significant increase in bowel activity may induce preterm labour.

Appendicitis

Pregnant women may lack classic symptoms and signs of appendicitis due to the anatomical and physiological changes that take place during pregnancy. As a result of this, the diagnosis may be delayed, particularly in the third trimester. The location of pain may vary depending on the gestation at the time of presentation; for example, pain may be located in the right lumbar region in early gestation or even in the right hypochondrium in late gestation. This may be due to displacement of the caecum and therefore the appendix by the gravid uterus. In early pregnancy, the pain starts in the paraumbilical region and then settles in the right iliac fossa. Both delayed intervention with perforation and unnecessary intervention increase mortality and morbidity for both the fetus and the mother. The timing of intervention varies by trimester: 90% of patients in the first trimester usually undergo an operation within 24 hours of the onset of symptoms, whereas in the third trimester 64% of patients will have symptoms for more than 48 hours before undergoing an

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Table 1.4 Summary of key changes in pregnancy and their clinical implications

	Physiological effects	Key clinical implications
Haematology	Hypercoagulable state Haemodilution of pregnancy	Predisposition for venous thromboembolism. Clots usually develop in the left leg or the left iliac venous system. The left side is most affected because the right iliac artery crosses the left iliac vein. The increased flow in the right iliac artery after birth compresses the left iliac vein, leading to an increased risk for thrombosis (clotting) which is exacerbated if there is lack of ambulation following delivery. The ↑ blood volume and the ↑ level of coagulation factors including fibrinogen and factors VII, VIII and X provide physiological protection against haemorrhage.
Cardiovascular system	Gravid uterus pressing over inferior vena cava Increased heart rate and stroke volume and cardiac output Reduced peripheral resistance	Aorto-caval compression – supine hypotension. In supine position, the vena cava is completely occluded in 90% of women and the stroke volume may be only 30% that of a non-pregnant woman. During cardiac arrest, to minimise the effects of the gravid uterus on venous return and cardiac output, a maternal pelvic tilt to the left of >15° is recommended. The tilt needs to be <30° for effective closed-chest compression to take place. Women with heart disease and fixed cardiac output may not cope with the demands and may develop pulmonary oedema. Fall in diastolic blood pressure.
Respiratory system	Oestrogen-induced oedema, hyperaemia and hypersecretion Minute ventilation increases in pregnancy because of increased tidal volume. 20% decrease in the functional residual capacity due to the pressure from the gravid uterus on the diaphragm and the lungs. This is exacerbated by 20% increase in their resting oxygen demand.	New-onset rhinitis, laryngeal oedema, hypertrophy of breasts → difficulty intubating pregnant women. Dyspnoea is experienced by up to 50% of pregnant women by 20 weeks and by 75% by 30 weeks. Relative state of hyperventilation causes a fall in $PaCO_2$ which results in chronic respiratory alkalosis. Mothers become hypoxic more readily.
Gastrointestinal system	Reduced lower oesophageal pressure, high intragastric pressure, delayed gastric emptying time Reduced colonic motility Course of IBD is not usually affected by pregnancy. Risk of flare is reduced if colitis is quiescent at the time of conception. Crohn's disease may experience postpartum flare.	Reflux oesophagitis; heartburn; constipation; risk of aspiration during general anaesthesia. In patients at term undergoing elective caesarean section, 49% are at risk of acid aspiration. Approximately 50% of women in labour have gastric pH < 2.5. Constipation is commonly seen in pregnancy. May prolong drug transit time. Prolonged contact time with the intestinal surface may result in a more complete absorption of drugs. If a drug is metabolised in the gut wall, less of the parent drug may reach the systemic circulation and therefore bioavailability will be reduced. Narcotic analgesics used in labour may further prolong gastric emptying and may result in accumulation of repeated medications leading to higher than desired levels. Women with IBD should be encouraged to conceive during periods of disease remission. Caesarean section may be indicated in the presence of severe peri-anal Crohn's disease. Active peri-anal Crohn's may prevent healing of an episiotomy.

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Table 1.4 (cont.)

	Physiological effects	Key clinical implications
Renal system	Retroverted gravid uterus pressing on the urethral-vesical junction Dextro-rotation of uterus, pressure from gravid uterus; dilatation of ureters	Acute retention of urine in early pregnancy Small ureteric stones may be passed easily. Increased risk of pyelonephritis and difficulty in interpretation of radiological studies of the urinary collecting system of pregnant women. Treatment of asymptomatic bacteriuria reduces the incidence of pyelonephritis.
Endocrine system	Increased secretion of anti-insulin hormones – HPL, glucagon and cortisol by placenta Physiological changes in pregnancy can significantly affect pre-existing diabetes.	Glucose tolerance decreases progressively with increasing gestation → increased insulin requirements in established diabetics and development of abnormal glucose tolerance in gestation diabetics, in whom there is insufficient insulin secretion to compensate for the insulin resistance. Exacerbation of complications of diabetes such as nephropathy and retinopathy.
Skin	Hyperpigmentation	Spider naevi and palmar erythema are normally seen in pregnancy.

HPL, human placental lactogen; IBD, inflammatory bowel disease.

operation. This delay may increase perforation and abscess formation [1]. Perforation, the rate of which has been reported to be approximately 25%–40% during pregnancy, increases the rates of spontaneous abortion, preterm labour, perinatal morbidity and mortality [2]. The non-obstetric differential diagnoses include ovarian cyst accidents, degenerating fibroid, acute cholecystitis, pyelonephritis and ureteric calculi and will depend on the gestational age and the location of the appendix. In the first trimester, appendicectomy may be performed laparoscopically or through a classical McBurney's incision. However, a paramedian incision over the area of maximum tenderness may allow the best access and the option of extension should the need arise.

Glycosuria

As a result of increased GFR there is an increase in the amount of glucose delivered to the kidneys. Associated with this is a reduction in the renal threshold for glucose. During pregnancy about a third of women excrete more than 5.5 mmol of glucose in 24 hours (renal glycosuria), which is significantly higher than that excreted by non-pregnant women (up to 0.55 mmol/24 hours). Since most commonly available commercial glucose oxidase/peroxide paper strips have a sensitivity of approximately 5.5 mmol/L, they will identify glycosuria in between 5% and 50% of the pregnant population, depending on the timing and frequency of testing. The routine use of urinalysis for monitoring of glycaemic control during pregnancy is therefore unreliable.

Thyroid Function Tests

In general, thyroid-stimulating hormone (TSH) is useful in screening for thyroid disease. However, it can be misleading when used alone in individuals being monitored for known thyroid disease, women in the first trimester, those with hyperemesis gravidarum or in molar pregnancy. This is mainly due to human chorionic gonadotropin levels, which show thyrotropic (TSH-like) activity. In these situations free T3 or T4 levels should be obtained.

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Skin Changes

Certain changes occur in normal pregnancy that would otherwise suggest liver disease. Physical findings include spider angiomata and palmar erythema, probably due to elevated oestrogen levels.

Key Pitfalls

- Interpretation of blood results may be difficult due to physiological haemodilution and changes in plasma proteins.
- Most standard liver function tests are normal in pregnancy; the fall in plasma albumin (dilutional effect) and rise in alkaline phosphatase do not reflect any liver disorder.
- Even in renal impairment, serum creatinine may be within a 'normal range' due to haemodilution.

Key Pearls

- Because of the anatomical and physiological changes that take place in pregnancy, it is important to interpret the investigations in the context of the changed values. Pregnancy-specific reference ranges should be used in making clinical decisions.
- Women who have low levels of haemoglobin at the start of pregnancy should receive an iron supplement throughout pregnancy to compensate for the 'physiological anaemia' of pregnancy.
- Considerable problems are recognised in the accurate measurement of blood loss and a definition based on volume alone has some shortcomings. Both visual and measured loss can be highly inaccurate. Underestimation of blood loss may delay active steps being taken to prevent further bleeding.
- Pregnancy increases the risk of venous thromboembolism (VTE). Assessment of pregnant women for development of risk factors during the course of pregnancy and postpartum is crucial to take appropriate measures to prevent/minimise the risk of VTE. D-Dimer does not carry the same significance as it would in non-pregnant women.
- Symptoms and signs of various medical conditions may not follow the same clinical pattern as in non-pregnant women, for example, appendicitis [3–5].
- Glucose: In pregnancy, the action of insulin is blunted; this unmasks latent diabetes and aggravates existing diabetes. The non-diabetic mother has slightly lower than normal blood glucose levels.
- Because of a fall in plasma albumin levels in pregnancy, drugs which are highly bound to albumin may be found in reduced levels in the bound fraction, with a corresponding increase in the free drug concentration. It is important to consider these effects while prescribing certain drugs.

Recent Developments

Recently, it has been shown that pregnant women at risk of gestational diabetes mellitus between gestational weeks 26 and 28 had significantly increased measures of arterial stiffness compared to low-risk healthy controls [6]. Moreover, obese pregnant women had significantly higher systolic blood pressure, cardiac output and left ventricular mass index [7]. Diastolic dysfunction was present in 12.5% of controls and 41% of obese women [7]. Therefore, with increasing incidence of gestational diabetes and obesity in many parts of the world, it is essential to understand this altered physiology to optimise outcomes.

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