Chapter 10

Physiological changes of pregnancy

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Introduction

The physiological changes of pregnancy consist of adaptations designed to enable adequate oxygen and nutrient delivery to both the mother and developing fetus. Thorough understanding of these changes is essential to differentiate between normal physiological alterations of pregnancy and pathological abnormalities. Many physiological and biochemical changes of pregnancy can modify the reference ranges of common laboratory results during different trimesters. Using reference ranges derived from non-pregnant women to evaluate and interpret laboratory values in pregnant women may lead to erroneous clinical implications. This chapter, therefore, reviews the major physiological adaptations during pregnancy and also highlights changes in the reference ranges of common laboratory values encountered in pregnancy.

Body fluid homeostasis

The expansion in total body fluid volume is one of the most significant changes during pregnancy, and this increase is distributed throughout the maternal–fetal unit. At term, the overall increase in body fluid volume is estimated to be 6.5 to 8.5 L [1]. While the fluid volume of the fetus, placenta, and amniotic cavity account for about 3.5 L, maternal blood volume increases 1.5–1.6 L, of which 1.2–1.3 L is plasma volume and 0.3–0.4 L is red blood cell volume [1,2]. The rest is attributed to the expansion of maternal extracellular fluid volume, breast as well as adipose tissue [1].

Immediately following conception, expansion of the plasma volume begins; this, in turn, decreases serum osmolality [1,3]. At 12 weeks of gestational age, serum osmolality is 8 to 10 mOsm/kg lower than the non-pregnant state [3]. In addition, the osmotic threshold for thirst and antidiuretic hormone release is lowered by 10 mosmol, resulting in increased water intake and retention [3]. Over the course of an entire pregnancy, 500–900 mmol sodium and 350 mmol potassium are usually retained. However, despite retention, the mean sodium and potassium concentrations are lower (3–4 mEq/L (mmol/L) and 0.2 mEq/L (mmol/L), respectively) after 12 weeks of gestational age compared with the non-pregnant state [3]. This decrease in the serum sodium and potassium concentrations is attributed to water retention, which exceeds sodium and potassium retention [3]. Table 10.1 summarizes the effects of maternal plasma volume expansion on the reference values of common serum electrolytes during pregnancy.

Cardiovascular system

Pregnancy induces a myriad of changes in the cardiovascular system, which include changes in cardiac output, heart rate, blood pressure, vascular compliance, capacitance, vascular resistance, and ventricular dimensions [5]. Many of these changes are thought to be caused by the hormonal milieu of pregnancy, and they may occur as early as 4–5 weeks of gestational age [6].

Maternal heart rate increases 10 to 20 beats/min over the course of pregnancy, peaking in the early third trimester, which in combination with a 25% increase in stroke volume, produces a 50% increase in overall cardiac output (i.e. heart rate multiplied by stroke volume) (Figure 10.1). Most of this increased cardiac output is directed towards the gravid uterus, placenta, and breasts. At term, the uterus and breasts receive 17% and 2% of cardiac output, respectively [1].

Labor and the immediate puerperium are associated with additional increases in cardiac output, which increases 12% in the first stage of labor and is primarily mediated by an increase in stroke

Maternal Critical Care: A Multidisciplinary Approach, ed. Marc Van de Velde, Helen Scholefield, and Lauren A. Plante. Published by Cambridge University Press.

Table 10.1. Reference ranges of serum electrolytes in pregnancy

Serum electrolyte	Non-pregnant adult	First trimester	Second trimester	Third trimester
Bicarbonate (mEq/L or mmol/L)	21–30	20–24	20–24	20–24
Calcium, ionized (mmol/L [mg/dL])	1.1–1.4 (4.5–5.6)	1.1–1.3 (4.5–5.1)	1.1–1.2 (4.4–5.0)	1.1–1.3 (4.4–5.3)
Calcium, total (mmol/L [mg/dL])	2.2–2.6 (9.0–10.5)	2.2–2.6 (8.8–10.6)	2.0–2.2 (8.2–9.0)	2.0–2.4 (8.2–9.7)
Chloride (mEq/L or mmol/L)	98–106	101–105	97–109	97–109
Magnesium (mmol/L [mg/dL])	0.8–1.2 (1.8–3.0)	0.7–0.9 (1.6–2.2)	0.6–0.9 (1.5–2.2)	0.4–0.9 (1.1–2.2)
Osmolality (mOsm/kg or mmol/kg serum water)	285–295	275–280	276–289	278–280
Phosphate (mmol/L [mg/dL])	1.0–1.4 (3.0–4.5)	1.0–1.5 (3.1–4.6)	0.8–1.5 (2.5–4.6)	0.9–1.5 (2.8–4.6)
Potassium (mEq/L or mmol/L)	3.5–5.0	3.6–5.0	3.3–5.0	3.3–5.1
Sodium (mEq/L or mmol/L)	136–145	133–148	129–148	130–148

Sources: Kratz, *et al*., 2004 [3]; Abbassi-Ghanavati, *et al*., 2009 [4].

volume [1]. This increase is thought to occur as a result of increased preload from additional blood expressed from the uterus during each contraction, a phenomenon sometimes called "uterine autotransfusion" [6]. During the second stage of labor, cardiac output can increase by up to 34%, with an initial increase from an increase in stroke volume following which additional increase in cardiac output mainly reflects increased heart rate [1]. Immediately postpartum (i.e. 10 to 30 minutes following delivery), approximately 300–500 mL of blood, which had previously been shunted to the uterus, is transferred to the maternal circulation, [6,7]. This increase in preload and stroke volume leads to a further increase in cardiac output by 10–20% [6]. This represents a particularly delicate time for patients with underlying cardiovascular disease for the development of pulmonary edema or congestive heart failure. Cardiac output values then return to pre-pregnancy levels by 2 weeks postpartum and to non-pregnant levels by 6 weeks postpartum [6,7].

Cardiac output is also affected by maternal position, with greatest output noted in knee–chest or lateral recumbent positions [1]. The gravid uterus compresses the inferior vena cava in the supine position and may completely occlude venous return from the lower extremities. Of note, 5–10% of pregnant women may experience nausea, diaphoresis, lightheadedness, or even syncope because of the supine position, which can be alleviated by gentle leftward tilt [1].

Progesterone-mediated smooth muscle relaxation causes vasodilatation and a fall in systemic vascular resistance by approximately 20% [1]. This effect begins at 5 weeks and will nadir between 20 and 32 weeks of gestation, after which systemic vascular resistance will gradually rise until term [1]. The decrease in systemic vascular resistance manifests as decreased blood pressure, even in light of increased cardiac output. Diastolic blood pressure decreases by 12 mmHg in mid-pregnancy, followed by a gradual increase of 10 mmHg by term [3]. Systolic blood pressure shows minimal change until a slight rise at 36 weeks of gestational age [3]. Therefore, the mean arterial blood pressure nadirs by mid-gestation, returning to pre-pregnancy levels by term [1,3].

Although all four chambers of the heart will increase in some size from the first trimester to the end of the third trimester, left ventricular hypertrophy and dilatation are particularly significant [1,3]. An increase in left ventricular end-diastolic volume can be seen by 10 weeks of gestation that peaks in the third trimester (Figure 10.1). The structural changes of the left ventricle are consistent with eccentric hypertrophy, which are similar to changes in exercise [1,9]. This is in contrast to concentric hypertrophy, which is usually seen as a long-term adaption to chronic hypertension. Eccentric hypertrophy enhances the efficiency and pumping capacity of the heart in the context of increased left end-diastolic volumes.

Central hemodynamic measurement may sometimes become necessary for critically ill pregnant

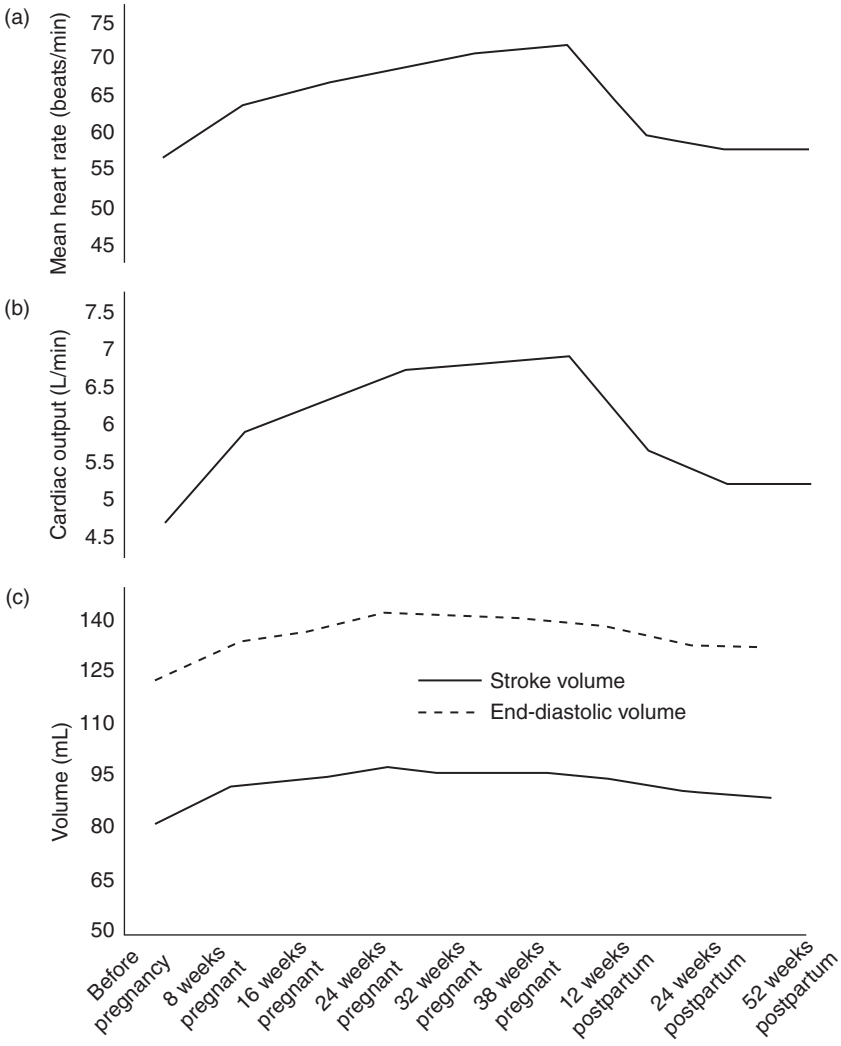

Figure 10.1. Variations in heart rate (a), cardiac output (b), stroke volume, and end-diastolic volume (c) before, during, and after pregnancy [6].

patients. Table 10.2 summarizes central hemodynamic measurements obtained via arterial lines and Swan–Ganz catheters in term pregnancies [8]. Pulmonary edema may develop when pulmonary capillary wedge pressure exceeds a threshold of 24 mmHg, and also when it exceeds the colloid oncotic pressure by more than 4 mmHg [1,8]. However, because colloid oncotic pressure decreases in pregnancy, pregnant patients may develop pulmonary edema at lower pulmonary capillary wedge pressures.

Respiratory system

Marked changes occur in the structure and function of the respiratory system during pregnancy. Apart from connective tissue changes in the upper airway and thorax, pregnancy affects static lung volumes, gas exchange, and ventilation [9].

The upper respiratory tract becomes edematous, hyperemic, congested, and friable at the beginning of the first trimester [9,10]. These changes, which are thought to be mediated by estrogen, persist throughout pregnancy, and peak in the third trimester [9,10]. The effects of estrogen on the nasal mucosa may explain why 30% of pregnant women experience rhinitis-like symptoms during pregnancy, as well as occasional nosebleeds [9].

The enlarging uterus constantly changes the configuration and dimensions of the thoracic cavity during pregnancy [1,9]. With progressive increases in uterine size, the circumference of the abdomen and lower chest wall increases, the costal angles widen, and

Table 10.2. Central hemodynamic measurements in normal term pregnancies

Hemodynamic measurement	Term pregnancy (36–38 weeks of gestation)	Change from non-pregnant state
Heart rate (beats/min)	83 ± 10	↑
Cardiac output (L/min)	6.2 ± 1	↑
Systemic vascular resistance (dyne.s/cm^5)	1210 ± 266	↓
Colloid oncotic pressure (mmHg)	18 ± 1.5	↓
Pulmonary capillary wedge pressure (mmHg)	3.6 ± 2.5	No change
Central venous pressure (mmHg)	3.6 ± 2.5	No change

Source: Clapp and Capeless, 1997 [5].

Table 10.3. Changes in static lung volumes observed during pregnancy

Lung volume	Definition	Change in pregnancy
Tidal volume	Volume of air inspired and expired in a normal breath	↑ (30 to 40%)
Inspiratory reserve volume	Maximum volume of air that can be inspired at the end of a normal inspiration	No change
Expiratory reserve volume	Maximum volume of air that can be expired at the end of a normal expiration	↓ (15–20%)
Inspiratory capacity	Maximum volume of air that can be inspired at the end of a normal expiration	↑ (5–10%)
Vital capacity	Maximum volume of air that can be forcibly expired after a maximal inspiration	No change
Functional residual capacity	Volume of air remaining in the lungs at the end of a normal expiration	↓ (17–20%)
Residual volume	Volume of air remaining in the lungs at the end of a maximal expiration	↓ (20–25%)
Total lung capacity	Total volume of air in the lungs at the end of a maximal expiration	No change to ↓ (5%)

Sources: Gabbe, *et al*., 2012 [1]; Crapo, 1996 [8]; Bobrowski, 2010 [9].

the resting position of the diaphragm elevates [9]. During pregnancy, both the anterior–posterior and transverse diameters of the chest wall increase, leading to an overall increase of 5–7 cm of the circumference of the lower chest wall [9]. The costal angles also widen by 50%, from 68° to 103° [9,10]. Furthermore, the resting position of the diaphragm is elevated 4–5 cm [9,10]. Although most of these changes are primarily mechanical effects of the enlarging uterus, relaxation of the ligamentous attachments to the ribs may contribute to earlier changes in the shape of the thoracic cavity [9,10]. Changes in the configuration of the thoracic cavity appear to peak at about 37 weeks of gestation, returning to normal dimensions within 24 weeks following delivery [9].

Structural changes of the thoracic cavity can translate into functional changes of the respiratory system, particularly static lung volumes. The functional residual capacity (FRC) decreases 300 to 500 mL (i.e. 17–20%), and this decrease is a direct effect of the elevated resting position of the diaphragm. The FRC can be further subdivided into expiratory reserve volume and residual volume, which decrease 100–300 mL (15–20%) and 200–300 mL (20–25%), respectively. The reduction in FRC causes a concomitant increase in the inspiratory capacity volume by 100–300 mL (5–10%) [9,10]. This decrease in FRC is clinically important as it increases the uptake and clearance of inhaled anesthetic agents [10].

Although some lung volumes are affected by the pregnancy-related changes of the thoracic cavity, the total lung capacity and vital capacity remain relatively unchanged by pregnancy [10]. Similarly, spirometric measurements reveal unchanged bronchial flow, suggesting that airway function remains stable during pregnancy [1,10]. Table 10.3 summarizes the changes in static lung volumes observed during pregnancy.

Oxygen consumption increases in pregnancy by up to 20% to meet the increasing metabolic demands of the mother and developing fetus. Logically, multifetal gestation increases oxygen consumption even more [10]. Additionally, during labor, oxygen consumption may increase by up to 60% [10]. Increasing progesterone levels stimulate the respiratory center of the medulla, causing an increase in the respiratory drive [1,10]. By 8 weeks of gestation, the minute ventilation increases 30 to 50%, primarily owing to a 40% increase in tidal volume (minute ventilation = tidal volume × respiratory rate) (Table 10.3) [1,10].

Table 10.4. Variations in arterial blood gas values in a term pregnancy

Blood gas measurement	Non-pregnant adult	Third trimester
pH	7.38–7.44	7.39–7.45
Arterial partial pressure of oxygen (mmHg [kPa])	80–100 (11–13)	92–107 (12.3–14.3)
Arterial partial pressure of carbon dioxide (mmHg [kPa])	35–45 (4.7–5.9)	25–33 (3.3–4.4)
Bicarbonate (mmol/L or mEq/L)	21–30	16–22

Sources: Clark, *et al*., 1989 [7]; Crapo, 1996 [8].

The increase in minute ventilation, combined with a physiological decrease in FRC, leads to a 50–70% increase in alveolar ventilation, thereby increasing alveolar oxygen partial pressure (P_{AO_2}), decreasing arterial carbon dioxide partial pressure (Pa_{CO_2}), and mildly increasing blood pH [1,9,10]. Decreased Pa_{CO_2} is critical in maintaining a carbon dioxide gradient that facilitates its transfer from the fetus to the mother. In addition, lower Pa_{CO_2} leads to mild respiratory alkalosis, with renal compensation occurring by increased bicarbonate excretion [1,9,10]. Variations in arterial blood gas values in a term pregnancy are summarized in Table 10.4. Because of increased oxygen consumption and decreased FRC, the maternal oxygen reserve is reduced; therefore, pregnant women are more susceptible to effects of apnea, particularly during intubation [1]. Hence, preoxygenation prior to intubation becomes necessary to prevent acute hypoxia and respiratory acidosis.

Pregnancy is also associated with changes in sleep patterns and sleep disorders that may continue postpartum. Although a detailed discussion of pregnancy-associated sleep patterns and disorders is beyond the scope of this chapter, several key points are worth highlighting. First, pregnancy is associated with an overall decrease in rapid-eye movement (REM) sleep and stage 3 and 4 non-REM sleep [1,10]. Second, with increasing gestational age, sleep efficiency and continuity decrease, while daytime somnolence and night-time awakenings increase [1]. Third, women who complain of excessive daytime sleepiness, night-time awakening, loud snoring, or self-reported or witnessed apneic spells must be evaluated with polysomnography for obstructive sleep apnea [1,10]. As obstructive sleep apnea leads to chronic hypoxemia, women with this apnea are at an increased risk of developing intrauterine growth restriction and gestational hypertension [1,10]. Finally, pregnancy may cause restless leg syndrome, a neurological disorder that can prevent women from falling asleep [1]. Although the prevalence of restless leg syndrome in pregnancy is not known, up to 23% of pregnant women may develop some component of this disorder in the third trimester [1].

Gastrointestinal and hepatobiliary systems and nutrition

Pregnancy-related hormones substantially influence the motility and synthetic function of the gastrointestinal and hepatobiliary systems. Modifications of these functions may manifest as clinical symptoms during pregnancy or may cause variations in the results of common laboratory values.

Nausea and vomiting are perhaps the most common symptoms experienced, possibly complicating up to 70% of pregnancies [1]. These symptoms typically peak at 9 weeks of gestation, with 60% resolving by the end of the first trimester, and 90% by 20 weeks of gestation [11]. Although the precise physiological mechanisms underlying nausea and vomiting remain unclear, rising human chorionic gonadotropin levels causing estrogen production is thought to be the most likely mechanism [11]. In most women, these symptoms resolve with minimal support; however, a small minority may suffer from hyperemesis gravidarum, a condition associated with persistent vomiting, profound dehydration, electrolyte imbalance, and weight loss, necessitating hospitalization [1,11].

As pregnancy progresses, many women experience gastroesophageal reflux caused by a combination of progesterone-mediated reduction in gastroesophageal sphincter tone and gastric compression by the enlarging uterus [1,3]. Progesterone and estrogen also decrease gastrointestinal motility, tone, and gall bladder emptying, resulting in modification of bowel habits and propensity to develop biliary sludge and stones [1,3].

Despite minimal change in the absolute blood flow to the liver during pregnancy, its synthetic capacity and activity increases several fold [3]. In addition to increased production of serum albumin, prealbumin and total protein, hepatic synthesis of fibrinogen, transferrin, ceruloplasmin, and the binding proteins for sex steroids, corticosteroids, and thyroid hormones

Table 10.5. Variations in the measured concentrations of markers of hepatic synthetic activity

Serum analyte	Non-pregnant adult	First trimester	Second trimester	Third trimester
Alanine transaminase (U/L [μkat/L])	0–35 (0–0.58)	3–30 (0.05–0.5)	2–33 (0.03–0.55)	2–25 (0.03–0.42)
Albumin (g/L)	35–55	31–51	26–45	23–42
Alkaline phosphatase (U/L [nkat/L])	30–120 (0.5–2.0)	17–88 (0.28–1.47)	25–126 (0.42–2.1)	38–229 (0.63–3.82)
Alpha-1 antitrypsin (g/L)	0.8–2.1	2.2–3.2	2.7–3.9	3.3–4.9
Asparatate transaminase (U/L [μkat/L])	0–35 (0–0.58)	3–23 (0.05–0.38)	3–33 (0.03–0.55)	4–32 (0.07–0.53)
Bilirubin, total (mmol/L [mg/dL])	5.1–17.0 (0.3–1.0)	1.7–6.8 (0.1–0.4)	1.7–13.7 (0.1–0.8)	1.7–18.8 (0.1–1.1)
Bilirubin, unconjugated (mmol/L [mg/dL])	1.7–5.1 (0.1–0.3)	1.7–8.5 (0.1–0.5)	1.7–6.8 (0.1–0.4)	1.7–8.5 (0.1–0.5)
Bilirubin, conjugated (mmol/L [mg/dL])	3.4–12.0 (0.2–0.7)	0–1.7 (0–0.1)	0–1.7 (0–0.1)	(0–1.7 (0–0.1)
Ceruloplasmin (mg/L)	270–370	300–490	400–530	430–780
Gamma-glutamyl transpeptidase (U/L)	1–94	2–23	4–22	3–26
Lactate dehydrogenase (U/L [μkat/L])	100–190 (1.7–3.2)	78–433 (1.3–7.2)	80–447 (1.3–7.5)	82–524 (1.4–8.7)
Prealbumin (mg/L)	195–358	150–270	200–270	140–230
Protein, total (g/L)	55–80	62–76	57–69	56–67

Sources: Kratz, *et al*., 2004 [3]; Abbassi-Ghanavati, *et al*., 2009 [4].

increases during pregnancy [1,3]. It is estimated that albumin mass increases by 15% to 123 g at 28 weeks of gestation compared with 107 g in the non-pregnant state [3]. Alkaline phosphatase levels also increase dramatically after 24 weeks of gestation, although this is attributed to a heat-stable isoenzyme produced from the placenta [1,3]. The measured levels of other liver enzymes, however, remain unchanged during pregnancy. Circulating estrogen can influence bile acid production and secretion, leading to mild subclinical cholestasis, even though fasting levels of bile acids remain unaffected by pregnancy [1]. These variations in commonly reported laboratory results are highlighted in Table 10.5.

Some women may exhibit unique clinical and laboratory findings that, although are within the physiological norms of pregnancy, may otherwise be considered as signs of liver disease. These include estrogen-related spider angiomata and palmar erythema, which resolve soon after delivery, as well as lowered serum albumin and total protein concentrations [1,3]. Although the overall concentrations of serum albumin and total protein increase during pregnancy, dilutional effects of the expanded plasma volume will lower measured concentrations (Table 10.5) [1,3]. The decreased serum albumin concentration may be reflected in the measurement of albumin-bound substances such as unconjugated bilirubin, calcium, and zinc, even though their total circulating levels may be higher (Table 10.5) [3].

In the absence of clinically significant nausea and vomiting, most women experience increased appetite, with caloric intake increasing by almost 300 kcal/day [1]. Pica, a peculiar craving for odd food such as iron, clay, detergent, or ice, may also occur [1]. In addition, many women may also complain of increased salivation. This condition, also known as ptyalism, may lead to losses of 1–2 L of saliva per day and actually represents the inability of nauseated women to swallow normal amounts of saliva rather than a true overproduction of saliva [1].

Cholesterol and triglyceride concentrations also change throughout pregnancy [3]. By 12 weeks of gestation, high density lipoprotein-cholesterol levels have increased by 20% compared with non-pregnant levels and continue to increase until term [3]. Similarly, low density lipoprotein-cholesterol levels begin to increase at 18 weeks of gestation, continuing to term [3]. Triglyceride levels increase by 40% at 18 weeks of gestational age, and are almost 250% higher than non-pregnant levels at term [3]. Table 10.6 summarizes the changes in lipid, cholesterol and triglycerides levels during pregnancy.

Adequate quantities of vitamins and certain trace minerals are necessary to ensure proper growth and

Table 10.6. Lipid, vitamin and mineral concentrations during pregnancy

Serum analyte	Non-pregnant adult	First trimester	Second trimester	Third trimester
Cholesterol, total (mmol/L [mg/dL])	<5.17 (<200)	3.65–5.44 (141–210)	4.56–7.74 (176–299)	5.67–9.04 (219–349)
High density lipoprotein-cholesterol (mmol/L [mg/dL])	1.03–1.55 (40–60)	1.03–2.02 (40–78)	1.35–2.25 (52–87)	1.24–2.25 (48–87)
Low density lipoprotein-cholesterol (mmol/L [mg/dL])	<2.59 (<100)	1.55–3.96 (60–153)	1.99–4.77 (77–184)	2.62–5.80 (101–224)
Very low density lipoprotein-cholesterol (mmol/L [mg/dL])	0.16–1.04 (6–40)	0.26–0.47 (10–18)	0.34–0.60 (13–23)	0.54–0.93 (21–36)
Triglyceride (mmol/L [mg/dL])	<1.8 (<160)	1.0–4.1 (40–159)	1.9–9.9 (75–382)	3.4–11.7 (131–453)
Apolipoprotein A1 (g/L)	1.2–2.4	1.1–1.5	1.4–2.5	1.4–2.6
Apolipoprotein B (g/L)	0.52–1.63	0.58–0.81	0.66–1.88	0.85–2.38
Retinol (vitamin A) (μmol/L [μg/dL])	0.7–3.5 (20–100)	1.1–1.6 (32–47)	1.2–1.5 (35–44)	1.0–1.5 (29–42)
Vitamin B_{12} (pmol/L [ng/dL])	205–712 (27.9–96.6)	87–323 (11.8–43.8)	96–484 (13.0–65.6)	73–388 (9.9–52.6)
Ascorbic acid (vitamin C) (μmol/L [mg/dL])	23–57 (0.4–1.0)	Not reported	Not reported	51–74 (0.9–1.3)
1,25-Dihydroxyvitamin D (pmol/L [ng/dL])	60–108 (2.5–4.5)	52–169 (2.0–6.5)	187–416 (7.2–16.0)	156–309 (6.0–11.9)
25-Dihydroxyvitamin D (nmol/L [μg/dL])	25–169 (1.0–6.8)	45–67 (1.8–2.7)	25–55 (1.0–2.2)	25–45 (1.0–1.8)
Alpha-tocopherol (vitamin E) (μmol/L [mg/dL])	116–279 (0.5–1.8	162–302 (0.7–1.3	232–371 (1.0–1.6	302–534 (1.3–2.3
Copper (μmol/L [μg/dL])	11–22 (70–140)	18–31 (112–199)	26–35 (165–221)	20–38 (130–240)
Zinc (μmol/L [μg/dL])	11–18 (75–120)	9–13 (57–88)	8–12 (51–80)	8–12 (50–77)

Sources: Kratz, *et al*., 2004 [3]; Abbassi-Ghanavati, *et al*., 2009 [4].

development of the fetus. While retinol (vitamin A) is lower during pregnancy, α-tocopherol (vitamin E) levels parallel the increase in cholesterol [3]. Overall levels of 1,25-dihydroxyvitamin D increase in pregnancy, but 25-hydroxyvitamin D generally does not change [1,3]. Circulating concentrations of trace minerals are influenced by their respective carrier proteins and serum albumin levels. In this context, copper concentrations increase in pregnancy because of increased hepatic synthesis of ceruloplasmin [1,3]. By contrast, lowered zinc concentrations correlate with lowered serum albumin levels [1,3]. These trends in vitamin and mineral concentrations during pregnancy are also listed in Table 10.6.

Genitourinary system

Similar to the cardiovascular and respiratory systems, the genitourinary system undergoes several anatomical and functional changes during pregnancy. The size and weight of the kidney increases during pregnancy through an increase in interstitial volume, renal vasculature, and urinary dead space [1,12]. Substantial dilatation of the renal calyx, pelvis, and ureters occurs, which contributes to the urinary dead space [1,3,12]. Dilatation of the ureters and renal pelves begins by the 8 weeks of gestation and peaks during the second trimester, when the ureteric diameter may be up to 2 cm. Often, dilatation of the right ureter exceeds that of the left [1]. On occasion, the physiological findings of ureteral and pelvicaliceal dilatation may interfere with radiological evaluation of urinary tract obstruction [1]. Pregnancy is also marked by anatomical changes in the bladder, which include elevation of the trigone and increased vascular tortuosity throughout the bladder. These changes primarily cause an increased incidence of microscopic hematuria [1]. Furthermore, bladder capacity decreases

because of the enlargement of the uterus, leading to increased urinary frequency, urgency, and possibly stress incontinence [1].

Renal plasma flow increases gradually during the first half of pregnancy, reaching values that are 60–80% greater by mid-pregnancy. At term, renal plasma flow is about 50% greater than non-pregnant levels [3,12]. Similarly, the glomerular filtration rate rises 40–50% by 9–11 weeks of gestation, and this value is generally sustained until 36 weeks of gestation [3,12]. The net effect of these changes is represented by a decrease in plasma concentrations of creatinine, uric acid, and blood urea nitrogen. With creatinine clearance increasing to 150–200 mL/min in pregnancy, compared with 120 mL/min in the non-pregnant state, serum creatinine and blood urea nitrogen concentrations decrease concurrently [1,3]. Serum uric acid concentrations decline in early pregnancy as a result of the increased glomerular filtration rate, reaching a nadir by 24 weeks of gestation [1,3]. Shortly after, uric acid concentrations begin to rise and reach preconceptional levels by the end of pregnancy [1,3]. These changes in renal physiology are listed in Table 10.7.

Increased renal plasma flow and glomerular filtration rate also increase urinary excretion of glucose, amino acids, and protein [3,12]. As a result, glycosuria is common in most pregnant women, although the mechanism does involve modified tubular reabsorptive capability [1]. Pregnant women may also lose up to 2 g of amino acids per day, compared with <0.5 g in the non-pregnant state [3]. Similarly, total urinary protein and microalbumin excretion almost doubles, with upper limits of 300 mg for proteinuria and 30 mg for albuminuria considered the norm during pregnancy [1,3]. Urinary calcium excretion also increases steadily until term, reaching 8.75–15.5 mmol/day, compared with 2.5–6.25 mmol/day in non-pregnant women [1,3]. The physiological changes in urinary excretion are also summarized in Table 10.7. Importantly, changes in urinary excretion in conjunction with increased volume of distribution alter drug distribution during pregnancy, necessitating higher drug doses to compensate for urinary excretion.

Hematology and coagulation

During pregnancy, several changes occur in the maternal hematological system to support the growing maternal–fetal unit [2]. Total maternal blood volume increases by 1500 to 1600 mL, of which 1200 to 1300 mL is plasma volume and 300 to 400 mL is red blood cell volume [1,2]. Maternal blood volume begins to increase by 6 weeks of gestation, reaching its peak between 30 and 34 weeks of gestation, after which it plateaus until delivery [1,2]. The overall magnitude of maternal blood volume expansion is greater in multifetal gestations and multiparous women [3,9]. In contrast, lower than normal plasma volume expansion is known to be associated with intrauterine growth restriction as well as pre-eclampsia [3,9].

The necessity for red blood cell mass increase is obvious considering the increased physiological requirements of the developing maternal–fetal unit [2]. The mechanism of red blood cell production is complex and involves hormonal mediators such as erythropoietin, human placental lactogen, estrogen, and progesterone. Although red blood cell volume increases during pregnancy, this rate of increase differs from the rate of

Table 10.7. Variations in measured concentrations of serum and urine analytes reflecting renal physiological adaptations

Serum/urine analyte	Non-pregnant adult	First trimester	Second trimester	Third trimester
Creatinine (mmol/L [mg/dL])	38–69 (0.5–0.9)	30–53 (0.4–0.7)	30–61 (0.4–0.8)	30–69 (0.4–0.9)
Urea nitrogen (mmol/L [mg/dL])	3.6–7.1 (10–20)	2.5–4.3 (7–12)	1.1–4.6 (3–13)	1.1–3.9 (3–11)
Uric acid (mmol/L [mg/dL])	90–360 (1.5–6.0)	119–250 (2.0–4.2)	143–291 (2.4–4.9)	184–375 (3.1–6.3)
Calcium excretion, 24 hour (mmol)	<7.5	1.6–5.2	0.3–6.9	0.8–4.2
Creatinine excretion, 24 hour (mmol)	8.8–1.4	10.6–11.6	10.3–11.5	10.2–11.4
Potassium excretion, 24 hour (mmol)	25–100	17–33	10–38	11–35
Protein excretion, 24 hour (mg)	<150	19–141	47–186	46–185
Sodium excretion, 24 hour (mmol)	100–260	53–215	34–213	37–149

Sources: Kratz, *et al.*, 2004 [3]; Abbassi-Ghanavati, *et al.*, 2009 [4].

increase in the maternal plasma volume. As a result of the rapid increase in maternal plasma volume in early pregnancy and the later rise in the volume of red blood cells, the hematocrit falls by as much as 10% in the first trimester; this trend continues through the second trimester, finally stabilizing near term [1,2]. This apparent decrease in hematocrit and hemoglobin concentrations during pregnancy is often called the "physiological anemia of pregnancy" [1,2].

Following delivery and blood loss, maternal blood volume does not re-expand or redistribute to predelivery levels. Instead, an overall diuresis of the expanded plasma volume occurs in the postpartum period [1]. This results in a gradual increase in hematocrit and normalization of maternal blood volume [2]. If hematocrit and hemoglobin concentrations at 5–7 days following delivery remain considerably lower than predelivery levels, then either the magnitude of blood loss was underestimated or the degree of pregnancy-induced blood volume expansion was low – or possibly both [1,2].

In a normal pregnancy, the peripheral white blood cell count starts to increase by mid-first trimester, reaching its peak by 30 weeks of gestation [1,2]. White blood cell count increases with the onset of labor, possibly reaching levels of up to 25×10^9/L to 30×10^9/L [2] (Table 10.8). This physiological increase in white blood cell count is primarily caused by an increase in circulating numbers of segmented neutrophils and granulocytes [1,2]. Care should be taken when interpreting the white blood cell count to determine the presence of an infection, particularly during labor. Counts return to non-pregnant levels within 1–2 weeks following delivery [1,2].

Prior to the introduction of automated analyzers, studies of platelet counts during pregnancy revealed conflicting results [1,12]. However, even after the introduction of automatic counting machines, studies remained non-confirmatory, primarily due to discrepancies in methodology and variations in study populations [1,2]. Despite these limitations, several experts

Table 10.8. Variations in red blood cells, white blood cells, platelets, and other hematological analytes during pregnancy

Hematological analyte	Non-pregnant adult	First trimester	Second trimester	Third trimester
Erythropoietin (IU/L)	4–27	12–25	8–67	14–222
Ferritin (μg/L)	10–200	6–130	2–230	0–116
Folate, red blood cell (nmol/L [μg/dL])	340–1020 (15.0–45.0)	310–1335 (13.7–58.9)	213–1876 (9.4–82.8)	247–1502 (10.9–66.3)
Folate, serum (nmol/L [μg/dL])	7.0–39.7 (0.31–1.75)	5.9–34.0 (0.26–1.50)	1.8–54.4 (0.08–2.40)	3.2–46.9 (0.14–2.07)
Hemoglobin (g/L)	120–160	116–139	97–148	95–150
Hematocrit (%)	36.0–46.0	31.0–41.0	30.0–39.0	28.0–40.0
Iron, serum (mmol/L [μg/dL])	5.4–28.7 (30–160)	12.9–25.6 (72–143)	7.9–31.9 (44–178)	5.4–34.6 (30–193)
Mean corpuscular hemoglobin (pg/cell)	26–34	30–32	30–33	29–32
Mean corpuscular volume (μm^3 or fl)	80–100	81–96	82–97	81–99
Platelet count ($\times 10^9$/L)	165–415	174–391	155–409	146–429
Red blood cell count ($\times 10^9$/L)	4.00–5.20	3.42–4.55	2.81–4.	2.71–4.43
Red cell distribution width (%)	11.5–14.5	12.5–14.1	13.4–13.6	12.7–15.3
White blood cell count ($\times 10^9$/L)	4.5–11.0	5.7–13.6	5.6–14.8	5.9–16.9
Neutrophils ($\times 10^9$/L)	1.4–4.6	3.6–10.1	3.8–12.3	3.9–13.1
Lymphocytes ($\times 10^9$/L)	0.7–4.6	1.1–3.6	0.9–3.9	1.0–3.6
Monocytes ($\times 10^9$/L)	0.1–0.7	0.1–1.1	0.1–1.1	0.1–1.4
Eosinophils ($\times 10^9$/L)	0–0.6	0–0.6	0–0.6	0–0.6
Basophils ($\times 10^9$/L)	0–0.2	0–0.1	0–0.1	0–0.1

Sources: Kratz, *et al*., 2004 [3]; Abbassi-Ghanavati, *et al*., 2009 [4].

agree that the platelet count in pregnancy seldom falls below 150×10^9/L [1,2]. Although a mild decrease in platelet count (70×10^9/L to 150×10^9/L) may be seen in women with gestational thrombocytopenia, dramatic decreases in platelet counts may be seen in conditions such as pre-eclampsia, placental abruption, or HELLP syndrome [1,2]. Changes observed in RBC, WBC platelet count, and other hematological parameters during pregnancy are summarized in Table 10.8.

The anatomical and physiological changes that occur during pregnancy increase the risk of thromboembolic events by four- to five-fold compared with non-pregnant women; these changes are consistent with Virchow's triad: vessel wall injury, increased venous stasis, and hypercoagulability [1,13]. Increased venous status in the lower extremities primarily results from compression of the inferior vena cava and pelvic veins by the enlarging uterus [1,13]. Pregnancy also alters the delicate balance of procoagulant, anticoagulant, and fibrinolytic activity, leading to overall hypercoagulability; while factors I (plasma fibrinogen), VII, VIII, and X are markedly increased, factors II, V, and IX remain unchanged [1,13]. In addition, pregnancy causes a decrease in the fibrinolytic activity through an increase in plasminogen activator inhibitor 1 and 2 [1,13]. Similarly, a progressive decrease in the levels of total and free protein S is noted in pregnancy without alteration of protein C and antithrombin III [1,13]. These changes in activity of the coagulation system are summarized in Tables 10.9 and 10.10.

Table 10.9. Changes in coagulation factors during pregnancy

Coagulation factor	Change from non-pregnant state
Antithrombin III	No change
Plasma fibrinogen (factor I)	↑
Factor II	No change
Factor V	No change
Factor VII	↑
Factor VIII	↑
Factor IX	No change
Factor X	↑
Free protein S	↓
Plasminogen activator inhibitor 1	↑
Plasminogen activator inhibitor 2	↑
Protein C	No change
von Willebrand factor	↑

Source: American College of Obstetricians and Gynecologists, 2011 [13].

Endocrine system

Several biochemical and metabolic changes are mediated by the interaction of different protein and steroid hormones during pregnancy. These changes are not only necessary for early embryonic and later fetal growth but are also important in mobilizing energy stores and transporting nutrients during pregnancy. Hence, endocrine disorders during pregnancy can adversely affect maternal and fetal outcome [1,3]. Table 10.11 summarizes physiological alterations of hormone levels during different trimesters of pregnancy.

Adrenal glands

Pregnancy is associated with an overall increase in the serum concentrations of total cortisol, free cortisol, aldosterone, deoxycorticosterone, corticosteroid-binding globulin, and adrenocorticotropic hormone [1,3]. Although the weight of the adrenal glands do not change significantly during pregnancy, expansion of the zona fasciculate is observed [1]. Corticosteroid-binding globulin concentrations begin to increase during the second trimester and rise to twice non-pregnant levels by term; total and free cortisol concentrations show a parallel increase beginning early second trimester (Table 10.11) [3]. Diurnal pattern of cortisol production is maintained during pregnancy, with significantly higher values found in the morning than in the afternoon [1,3]. The adrenal gland is more responsive to adrenocorticotropic hormone during pregnancy, causing a greater rise in cortisol concentration for a given dose of adrenocorticotropic hormone [3]. Despite these changes, the urinary excretion of catecholamines, vanillylmandelic acid, and metanephrines do not change during pregnancy (Table 10.11) [3].

Pancreas

Pregnancy results in fasting hypoglycemia, postprandial hyperglycemia, and hyperinsulinemia [1]. Early in pregnancy, estrogen and progesterone stimulate islet cell enlargement, hyperplasia of beta-cells, insulin secretion, and increased sensitivity of peripheral

Table 10.10. Changes in the levels of coagulation factors during pregnancy

Coagulation factor	Non-pregnant adult	First trimester	Second trimester	Third trimester
Antithrombin III, functional (% [U/L])	80–130 (0.8–1.3)	89–114 (0.89–1.14)	88–112 (0.88–1.12)	82–116 (0.82–1.16)
D-dimer (mg/L)	<0.5	0.05–0.95	0.32–1.29	0.13–1.7
Plasma fibrinogen (factor I) (g/L)	1.5–4.0	2.44–5.1	2.91–5.38	3.73–6.19
Factor VII (%)	60–140	100–146	95–153	149–211
Factor VIII (%)	50–200	90–210	97–312	143–253
International normalized ratio	0.9–1.04	0.89–1.05	0.85–0.97	0.80–0.94
Partial thromboplastin time, activated (s)	22.1–35.1	24.3–38.9	24.2–38.1	24.7–35.0
Prothrobin time (s)	11.1–13.1	9.7–13.5	9.5–13.4	9.6–12.9
Protein C, functional (%)	70–140	78–121	83–133	67–135
Protein S, total (%)	70–140	39–105	27–101	33–101
Protein S, free (%)	70–140	34–133	19–113	20–65
Tissue plasminogen activator (μg/L)	1.6–13	1.8–6.0	2.4–6.6	3.3–9.2
Tissue plasminogen activator inhibitor 1 (μg/L)	4–43	16–33	36–55	67–92
Von Willebrand factor (%)	75–125	Not reported	Not reported	121–260

Sources: Kratz, *et al*., 2004 [3]; Abbassi-Ghanavati, *et al*., 2009 [4].

Table 10.11. Physiological alterations in different hormone levels during pregnancy

Hematological parameter	Non-pregnant adult	First trimester	Second trimester	Third trimester
Aldosterone (pmol/L [ng/dL])	55–250 (2–9)	166–1885 (6–104)	250–1885 (9–104)	416–2802 (15–101)
Angiotensin-converting enzyme (U/L [nkat/L])	<670 (<40)	1–38 (16–633)	1–36 (16–600)	1–39 (16–650)
Cortisol (nmol/L [μg/dL])	0–690 (0–25)	193–524 (7–19)	276–1159 (10–42)	331–1379 (12–50)
Estradiol (nmol/L [ng/dL])	0.07–1.63 (2.0–44.3)	0.69–9.17 (18.8–249.7)	4.69–26.40 (127.8–719.2)	22.53–127.0 (613.7–346.0)
Hemoglobin A1c (%)	3.8–6.4	4–6	4–6	4–7
Parathyroid hormone (ng/L)	10–60	10–15	18–25	9–26
Parathyroid hormone-related protein (pmol/L)	<1.3	0.7–0.9	1.8–2.2	2.5–2.8
Progesterone (nmol/L [μg/dL])	0.64–64 (0.02–2.0)	25.4–153 (0.8–4.8)	Not reported	315–1088 (9.9–34.2)
Prolactin (μg/L)	0–20	36–213	110–330	137–372
Sex hormone-binding globulin (nmol/L)	18–114	39–131	214–717	216–724
Thyroid-stimulating hormone (mU/L)	0.5–4.7	0.60–3.4	0.37–3.6	0.38–4.04
Thyroxine, free (pmol/L [ng/dL])	10.3–35.0 (0.8–2.7)	10.3–15.5 (0.8–1.2)	7.7–12.9 (0.6–1.0)	6.4–10.3 (0.5–0.8)

Sources: Kratz, *et al*., 2004 [3]; Abbassi-Ghanavati, *et al*., 2009 [4].

tissues to insulin [3]. The overall result is an anabolic state associated with increased glucose utilization, decreased gluconeogenesis, and increased glycogen storage [3]. In the latter half of pregnancy, however, rising levels of progesterone, cortisol, glucagon, human placental lactogen, and prolactin, along with decreased insulin receptor binding, contribute to insulin resistance [3]. After feeding, insulin resistance maintains high blood glucose levels, thereby enhancing glucose transport to the fetus [3]. These diabetogenic changes in some pregnant women may result in gestational diabetes [1,3].

Pituitary gland

Pituitary enlargement occurs in pregnancy by estrogen-mediated proliferation of prolactin-producing cells. This enlargement may render the pituitary gland more susceptible to alterations in blood supply, specifically increasing the risk for infarction in the context of excessive postpartum hemorrhage [1,3]. Serum prolactin levels begin to increase early first trimester and are 10 times higher at term. In non-lactating women, prolactin levels return to baseline by 3 months after delivery. However, in lactating women, this return may take several months and is influenced by the length and frequency of nursing [1]. Oxytocin levels increase throughout pregnancy: 10 ng/L in the first trimester, 30 ng/L in the third trimester, and 75 ng/L at term. These levels dramatically increase and peak during labor [1].

Thyroid

Pregnancy is an overall euthyroid state, although alterations in thyroid morphology and histology occur [1,3]. With adequate iodine intake, the size of the thyroid gland remains unchanged or increases slightly [1]. In addition, thyroid vascularity increases and histological evidence of follicular hyperplasia is noted [1]. However, the development of a goiter anytime during pregnancy is considered abnormal and should be evaluated [1,3].

During the first trimester of pregnancy, total thyroxine and total triiodothyronine concentrations begin to increase and peak at mid-gestation, primarily as a result of increased production of thyroid-binding globulin [1,3]. Free thyroxine concentrations, however, remain unchanged during the first trimester, after which there is a 25% decrease in mean concentrations during the second and third trimester [1,3]. Thyroid-stimulating hormone decreases transiently in the first trimester. Following this initial decrease, concentrations rise to non-pregnant levels by the end of the first trimester and then remain stable throughout the remainder of pregnancy [1,3]. The transient decrease in thyroid-stimulating hormone is thought be to mediated by the thyrotropic effects of human chorionic gonadotropin and coincides with the first trimester increase in free thyroxine [1,3].

Immunology

The immunological adaptations of pregnancy, particularly at the maternal–fetal interface, comprise complex mechanisms that enable the fetus to grow while preventing the mother from rejecting the fetus [1,14]. These mechanisms include fetal factors such as altered major histocompatibility complex class I expression as well as maternal factors such as uterine natural killer cells and a shifting of the T-helper cell cytokine profile from type 1 to type 2 [1,14]. This shift in T-helper type 1-mediated cellular immunity to type 2-mediated humoral immunity may explain why pregnant women are more susceptible to viral infections [1,14].

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