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Maternal Physiology

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The physiological changes of pregnancy are strongly proactive, not reactive, with the luteal phase of every ovulatory menstrual cycle 'rehearsing' for pregnancy. Most pregnancy-driven changes are qualitatively in place by the end of the first trimester, only maturing in magnitude thereafter [1]. This chapter gives a brief overview of the major changes.

Maternal response to pregnancy

Normal pregnancy evokes a systemic inflammatory response, which includes the endothelium [2]. This may explain the greater risk of cardiovascular disease in later life of parous women in comparison with nulliparous women. Markers of oxidative 'stress' rise progressively throughout the first and second trimesters, but plasma concentrations of some endogenous antioxidants, such as superoxide dismutase, rise in parallel. The free radical superoxide is generated through a variety of pathways, including placental ones, but is more damaging when converted to the peroxide radical, a reaction catalysed by free iron in the plasma. Increasing concern is being expressed about over-supplementation with iron, especially in conjunction with vitamin C (which increases absorption) in pregnant women without evidence of iron deficiency and several studies have shown evidence of increased oxidative stress in such women [3]. Conversely, the low dietary selenium intake in women in the UK may predispose to lower activity of the antioxidant glutathione peroxidase and thioredoxin systems in pregnancy.

Immunology

Only two types of fetal tissue come into direct contact with maternal tissues: the villous trophoblast and the extravillous trophoblast. Villous trophoblast, which is a continuous syncytium, is bathed in maternal blood but seems to be immunologically inert and never expresses HLA class I or class II molecules. Extravillous trophoblast is directly in contact with maternal endometrial/decidual tissues and does not express the major T-cell ligands, HLA-A or HLA-B; the HLA class I molecules which are expressed are the trophoblast-specific HLA-G and HLA-C and HLA-E. The decidual uterine natural killer (NK) cells, the main type of decidual lymphocyte, differ from those in the systemic circulation. They express surface killer immunoglobulin-like receptors (KIRs), which bind to HLA-C and HLA-G on trophoblast. HLA-E and HLA-G are effectively monomorphic, but HLA-C is polymorphic, with two main groups, HLA-C1 and HLA-C2. The KIRs are very highly polymorphic, but again fall into two main classes, KIR-A (non-activating) and KIR-B (multiply activating). Thus the very polymorphic KIR in maternal tissues and the polymorphic HLA-C in the fetus make up a potentially very variable receptor–ligand system.

The effect of this on implantation has been inferred from indirect evidence. Both recurrent miscarriage and pre-eclampsia are associated with poor trophoblast invasion. The maternal KIR genotype may be AA, AB or BB. Since the identifiable trophoblast HLA-C allotypes are HLA-C1 and HLA-C2, there are nine possible combinations. It has been shown that if the maternal KIR haplotype is AA, and the trophoblast expresses any HLA-C2, then the possibility of miscarriage or pre-eclampsia is significantly increased. However, even one KIR-B provides protection [4]. HLA-C2 is highly inhibitory to trophoblast migration, and thus appears to need 'activating KIR' to overcome it.

NK cells appear and disappear in the endometrial decidua every ovulatory menstrual cycle, and the populations are maintained should conception occur. When progesterone is at its peak, they associate with the spiral arteries and uterine glands. Human data are limited, and animal studies of immunological phenomena must be

viewed with especial caution in pregnancy, so the precise role of NK cells is not yet known. However, timed human endometrial sampling at 8–10 weeks' gestation has shown them to be major producers of a variety of angiogenic factors, expressing transcripts of *VEGFC* (vascular endothelial growth factor C), *PlGF* (placental growth factor) and *ANG2* (angiopoietin 2). This has ceased by 12–14 weeks. It has been suggested that NK cells are essential for spiral artery remodelling (for a review see Zhang *et al.* [5]).

The uterus

The first-trimester human embryo appears to gain nutrients histiotrophically, from the endometrial glands. These glandular secretions are rich in carbohydrates, lipids and growth factors and can well support early growth while the conceptus is small [6]. The inner third of the myometrium, as well as the endometrium, is anatomically changed by pregnancy, and once a pregnancy has gone beyond the first trimester, these changes appear to be irreversible. The most striking change is in the spiral arteries, which undergo extensive remodelling. Extravillous trophoblast attacks these vessels as interstitial cells within the stroma, and as endovascular cells within the vascular lumen. In normal pregnancy, the summed effects are the conversion of these vessels into floppy thin-walled vessels, more closely resembling veins than arteries, that do not respond to vasoconstrictor stimuli, so allowing the maximum flow to reach the placenta. This remodelling is only completed in the early second trimester, but is impaired in both pre-eclampsia and normotensive intrauterine growth restriction.

The uterus must be maintained in quiescence until labour is initiated. The mechanisms responsible for this have not been fully elucidated, although progesterone plays a central role, but include locally generated nitric oxide, probably acting through cyclic GMP or voltage-gated potassium channels such as Kv7 and Kv11, while a number of hormones such as brain natriuretic peptide, prostacyclin, prostaglandin (PG)E_2 and calcitonin gene-related peptide act through G_s receptors, and are relaxatory.

The cardiovascular system

There is much less information about the normal functioning of the cardiovascular system in young women than in young men, partly because they have been perceived as being 'more difficult' to study as a result of the monthly ovulatory cycle. However, an increasing number of studies have been initiated prior to conception and continuing
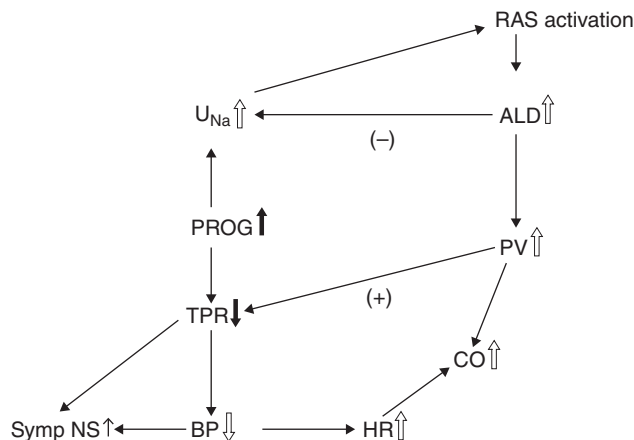

Fig. 1.1 Flow chart of the probable sequence of initial cardiovascular activation. ALD, aldosterone; BP, systemic arterial blood pressure; CO, cardiac output; HR, heart rate; PROG, progesterone; PV, plasma volume; RAS, renin–angiotensin system; Symp NS, sympathetic nervous system; TPR, total peripheral resistance; U_{Na}, urinary sodium excretion.

thereafter. These are very demanding, but also extremely valuable. Such studies also underline the inherent errors in using data obtained at the first antenatal clinic visit, often late in the first trimester, as true baseline.

There is a significant fall in total peripheral resistance by 6 weeks' gestation to a nadir of about 40% by mid-gestation, resulting in a fall in afterload. This is 'perceived' as circulatory underfilling, which activates the renin–angiotensin–aldosterone system and allows the necessary expansion of plasma volume (PV) (Fig. 1.1) [7,8]. By the late third trimester, the PV has increased from its baseline by about 50% in a first pregnancy and 60% in a second or subsequent pregnancy. The bigger the expansion, the bigger, on average, the birthweight of the baby. The total extracellular fluid volume rises by about 16% by term, so the percentage rise in PV is disproportionate to the whole. The plasma osmolality falls by about 10 mosmol/kg as water is retained.

The heart rate rises synchronously, by 10–15 bpm, so the cardiac output begins to rise [9]. There is probably a fall in baroreflex sensitivity as pregnancy progresses, and heart rate variability falls. Stroke volume rises a little later in the first trimester. These two factors push the cardiac output up by 35–40% in a first pregnancy, and by about 50% in later pregnancies; it can rise by a further third in labour (Fig. 1.2). Table 1.1 summarizes the percentage changes in some cardiovascular variables during pregnancy [9].

Measuring brachial systemic arterial blood pressure in pregnancy is notoriously difficult, but there is now broad consensus that Korotkoff 5 should be used with auscultatory techniques [10]. However measured, there is a small fall in systolic, and a greater fall in diastolic, blood

Fig. 1.2 Major haemodynamic changes associated with normal human pregnancy. The marked augmentation of cardiac output results from asynchronous increases in both heart rate (HR) and stroke volume (SV). Despite the increases in cardiac output, blood pressure (BP) decreases for most of pregnancy. This implies a very substantial reduction in total peripheral vascular resistance (TPVR).
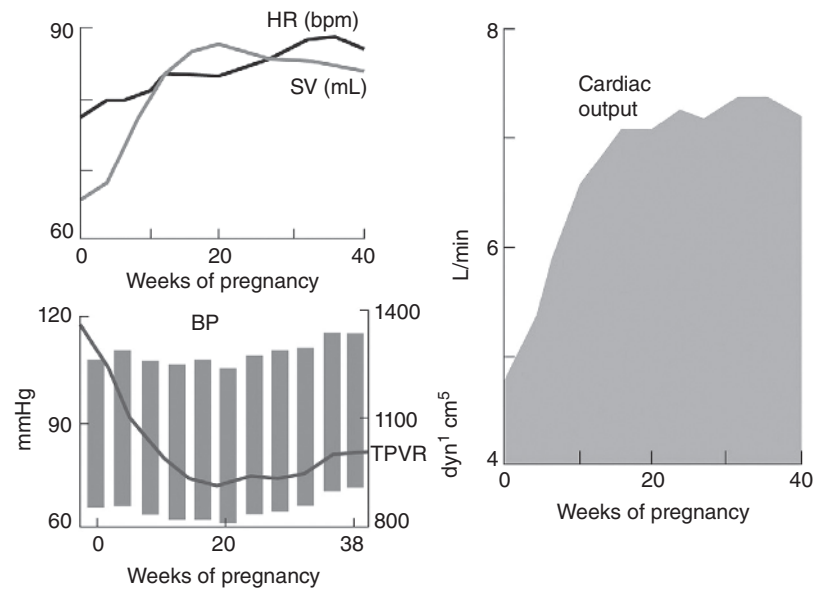
Table 1.1 Percentage changes in some cardiovascular variables during pregnancy.

	First trimester	Second trimester	Third trimester
Heart rate (bpm)	+11	+13	+16
Stroke volume (mL)	+31	+29	+27
Cardiac output (L/min)	+45	+47	+48
Systolic blood pressure (mmHg)	−1	−1	+6
Diastolic blood pressure (mmHg)	−6	−3	+7
MPAP (mmHg)	+5	+5	+5
Total peripheral resistance (resistance units)	−27	−27	−29

MPAP, mean pulmonary artery pressure. Data are derived from studies in which pre-conception values were determined. The mean values shown are those at the end of each trimester and are thus not necessarily the maxima. Note that most changes are near maximal by the end of the first trimester.

pressure, initiated during the luteal phase, being mainly complete by 6–7 weeks' gestation, but continuing more slowly to the late second trimester, resulting in an increased pulse pressure. The blood pressure then rises steadily, in parallel with an increase in peripheral sympathetic activity, and even in normotensive women there may be some late overshoot of non-pregnant values. Supine hypotension occurs in about 8% of women in late gestation as the uterus falls back onto the inferior vena cava, reducing venous return.

There is increasing interest in large artery function, measured as aortic pulse wave velocity (aPWV), and wave reflections, measured as the augmentation index (AIx). The central blood pressure can be estimated non-invasively, and has been suggested to be superior to the brachial blood pressure in predicting future adverse cardiovascular events outside pregnancy. Central blood pressure falls significantly more during the first 6 weeks of pregnancy than brachial blood pressure, but also reaches a nadir in the late second trimester. The AIx, adjusted for heart rate, falls significantly by 6–7 weeks' gestation, again reaching a nadir in the late second trimester; the aPWV, adjusted for mean blood pressure, does not change significantly [11].

The pressor response to angiotensin II is reduced in normal pregnancy but is unchanged to noradrenaline. The reduced sensitivity to angiotensin II presumably protects against the potentially pressor levels of angiotensin II found in normal pregnancy and is associated with lower receptor density; plasma noradrenaline is not increased in normal pregnancy. Pregnancy does not alter the response of intramyometrial arteries to a variety of vasoconstrictors. Nitric oxide may modulate myogenic tone and flow-mediated responses in the resistance vasculature of the uterine circulation in normal pregnancy.

The venous pressure in the lower circulation rises, for both mechanical and hydrodynamic reasons. The pulmonary circulation is able to absorb high rates of flow without an increase in pressure so pressure in the right ventricle, and the pulmonary arteries and capillaries, does not change. Pulmonary resistance falls in early pregnancy, and does not change thereafter. There is progressive venodilatation and rises in venous distensibility and capacitance throughout a normal pregnancy, possibly because of increased local nitric oxide synthesis.

The respiratory system

Tidal volume rises by about 30% in early pregnancy to 40–50% above non-pregnant values by term, with a fall in expiratory reserve and residual volume (Fig. 1.3) [12]. Neither forced expiratory volume in 1 s (FEV_1) nor peak expiratory flow rate are affected by pregnancy, even in women with asthma. The rise in tidal volume is largely driven by progesterone, which appears to decrease the threshold and increase the sensitivity of the medulla oblongata to carbon dioxide. Respiratory rate does not change, so the minute ventilation rises by a similar amount. This over-breathing begins in every luteal phase; the $P\text{CO}_2$ is lowest in early gestation. Progesterone also increases erythrocyte carbonic anhydrase concentration, which will also lower $P\text{CO}_2$. Carbon dioxide production rises sharply during the third trimester, as fetal metabolism increases. The fall in maternal $P\text{CO}_2$ allows more efficient placental transfer of carbon dioxide from the fetus, which has a $P\text{CO}_2$ of around 55 mmHg (7.3 kPa). The fall in $P\text{CO}_2$, together with an increased renal excretion of bicarbonate, results in a fall in plasma bicarbonate concentration (to about 18–22 mmol/L compared with the non-pregnant range of 24–28 mmol/L), which contributes to the fall in plasma osmolality and reduces buffering capacity. The peripheral venous pH rises slightly (Table 1.2 and Fig. 1.4).

The increased alveolar ventilation results in a much smaller proportional rise in $P\text{O}_2$ from about 96.7 to 101.8 mmHg (12.9–13.6 kPa). This increase is offset by the rightward shift of the maternal oxyhaemoglobin dissociation curve caused by an increase in 2,3-diphosphoglycerate (2,3-DPG) in the erythrocytes and the lower plasma bicarbonate concentration. This facilitates oxygen

Table 1.2 The influence of pregnancy on some respiratory variables.

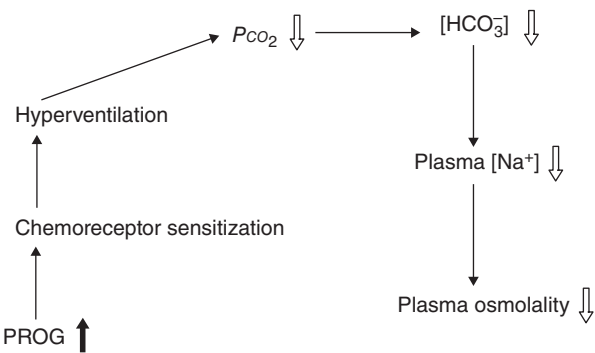|	Non-pregnant	Pregnant – term
$P\text{O}_2$ (mmHg)	93 (12.5 kPa)	102 (13.6 kPa)
O_2 consumption (mL/min)	200	250
$P\text{CO}_2$ (mmHg)	35–40 (4.7–5.3 kPa)	30 (4.0 kPa)
Venous pH	7.35	7.38

Fig. 1.4 Flow chart of the effects of over-breathing in pregnancy. HCO_3^-, bicarbonate; Na^+, sodium; $P\text{CO}_2$, carbon dioxide tension; PROG, progesterone.

unloading to the fetus, which has both a much lower $P\text{O}_2$ (25–30 mmHg, 3.3–4.0 kPa) and a marked leftward shift of the oxyhaemoglobin dissociation curve, due to the lower sensitivity of fetal haemoglobin to 2,3-DPG.

There is an increase of about 16% in oxygen consumption by term due to increasing maternal and fetal demands. Since the increase in oxygen-carrying capacity
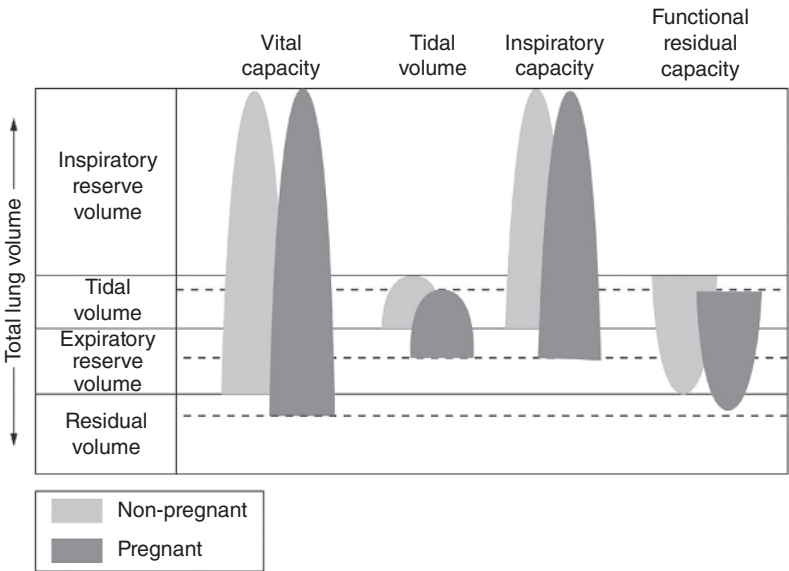

Fig. 1.3 Alterations in lung volumes associated with normal human pregnancy. In general terms, inspiratory reserve and tidal volumes increase at the expense of expiratory reserve and residual volumes.

Table 1.3 Although the increases in resting cardiac output and minute ventilation are of the same order of magnitude in pregnancy, there is less spare capacity for increases in cardiac output on moderate exercise than for increases in respiration.

	Resting	Exercise
Cardiac output	+33% (4.5–6 L/min)	+167% (up to 12 L/min)
Minute ventilation	+40% (7.5–10.5 L/min)	+1000% (up to ∼80 L/min)

of the blood (see section Haematology) is about 18%, there is actually a fall in arteriovenous oxygen difference. Pulmonary blood flow, of course, rises in parallel with cardiac output and enhances gas transfer.

Pregnancy places greater demands on the cardiovascular than the respiratory system [13]. This is shown in the response to moderate exercise (Table 1.3).

Haematology

The circulating red cell mass rises by 20–30% during pregnancy, with increases in both cell number and size. It rises more in women with multiple pregnancies, and substantially more with iron supplementation (∼29% compared with 17%). Serum iron concentration falls, the absorption of iron from the gut rises and iron-binding capacity rises in a normal pregnancy, since there is increased synthesis of the β_1-globulin transferrin. Nevertheless, 75% of diagnosed anaemia in pregnancy arises from iron deficiency. Plasma folate concentration halves by term, because of greater renal clearance, although red cell folate concentrations fall less. In the late 1990s, one-fifth of the female population aged 16–64 in the UK were estimated to have serum ferritin levels below 15 μg/L, indicative of low iron stores [14]; a similar proportion was reported in 2008 [15]. Pregnant adolescents seem to be at particular risk of iron deficiency. Even relatively mild maternal anaemia is associated with increased placental weight/birthweight ratios and decreased birthweight. However, inappropriate supplementation can itself be associated with pregnancy problems (see above) [16]. The National Institute for Health and Care Excellence (NICE) recommends that iron supplementation should be considered for women with haemoglobin concentrations below 110 g/L in the first trimester and 105 g/L at 28 weeks [17].

Erythropoietin rises in pregnancy, more so if iron supplementation is not taken (55% compared with 25%) but the changes in red cell mass antedate this; human placental lactogen may stimulate haematopoiesis.

Pro rata, the PV increases more than the red cell mass, which leads to a fall in the various concentration measures that incorporate the PV, such as the haematocrit, haemoglobin concentration and red cell count. The fall in packed cell volume from about 36% in early pregnancy to about 32% in the third trimester is a sign of normal PV expansion.

The total white cell count rises, mainly because of increased polymorphonuclear leucocytes. Neutrophil numbers rise with oestrogen concentrations and peak at about 33 weeks, stabilizing after that until labour and the early puerperium, when they rise sharply. Their phagocytic function increases during gestation. T and B lymphocyte counts do not change but their function is suppressed, making pregnant women more susceptible to viral infections, malaria and leprosy. The uterine NK cells express receptors that recognize the otherwise anomalous combination of human lymphocyte antigens (HLA-C, HLA-E and HLA-G) expressed by the invasive cytotrophoblasts. This is likely to be central to maternal recognition of the conceptus [18] (see above).

Platelet count and platelet volume are largely unchanged in most pregnant women, although their survival is reduced. Platelet reactivity is increased in the second and third trimesters and does not return to normal until about 12 weeks after delivery.

Coagulation

The changes in coagulation profile during pregnancy are most complex at the time of labour and delivery, with the urgent need to prevent life-threatening haemorrhage from the placental separation site, while avoiding excessive activation and thrombosis. Coagulation in pregnancy has recently been reviewed [19]. Continuing low-grade coagulopathy is a feature of normal pregnancy [20]. Several of the potent procoagulatory factors rise from at least the end of the first trimester [21] (Fig. 1.5). For example, factors VII, VIII and X all rise, and absolute plasma fibrinogen doubles, while antithrombin III, an inhibitor of coagulation, falls. The erythrocyte sedimentation rate rises early in pregnancy due to the increase in fibrinogen and other physiological changes. Protein C, which inactivates factors V and VIII, is probably unchanged in pregnancy, but concentrations of protein S, one of its cofactors, fall during the first two trimesters. An estimated 5–10% of total circulating fibrinogen is consumed during placental separation, and thromboembolism is one of the main causes of maternal death in the UK. Plasma fibrinolytic activity is decreased during pregnancy and labour, but returns to non-pregnant values within an hour of delivery of the placenta, suggesting strongly that the control of fibrinolysis during pregnancy is significantly affected by placentally derived mediators. Table 1.4 summarizes changes in some coagulation and fibrinolytic variables during pregnancy [22].
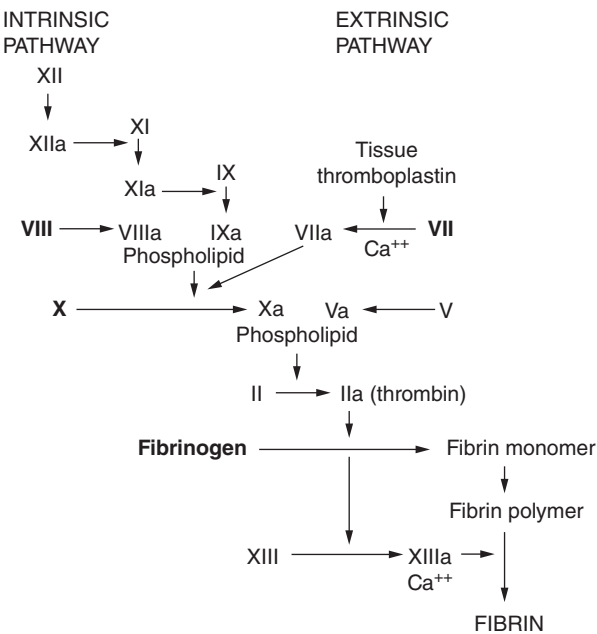
Fig. 1.5 Alterations in the coagulation pathways associated with human pregnancy. Factors which increase during normal pregnancy are in bold type. *Source:* Chamberlain, G. and Broughton Pipkin, F. *Clinical Physiology in Obstetrics*, 3rd edn. Oxford: Wiley, 1998. Reproduced with permission of John Wiley & Sons.

The renal system

The kidneys increase in size in pregnancy mainly because renal parenchymal volume rises by about 70%, with marked dilatation of the calyces, renal pelvis and ureters in most women [23]. Ureteric tone does not decrease, but bladder tone does. The effective renal plasma flow (ERPF) is increased by at least 6 weeks' gestation and rises to some 80% by mid-pregnancy falling thereafter to about 65% above non-pregnant values (Fig. 1.6). This increase is proportionally greater than the increase in cardiac output, presumably reflecting specific vasodilatation, probably via increased local prostacyclin or nitric oxide synthesis. The glomerular filtration rate (GFR) also increases, by about 45% by the ninth week, only rising thereafter by another 5–10%, but this is largely maintained to term, so the filtration fraction falls during the first trimester, is stable during the second, and rises thereafter, possibly to levels above non-pregnant. However, these major increments do not exhaust the renal reserve. The differential changes in ERPF and GFR in late pregnancy suggest a mechanism acting preferentially at the efferent arterioles, possibly through angiotensin II.

The filtered load of metabolites therefore increases markedly, and reabsorptive mechanisms frequently do not keep up (e.g. glucose and amino acids; see section Energy requirements). These changes have profound
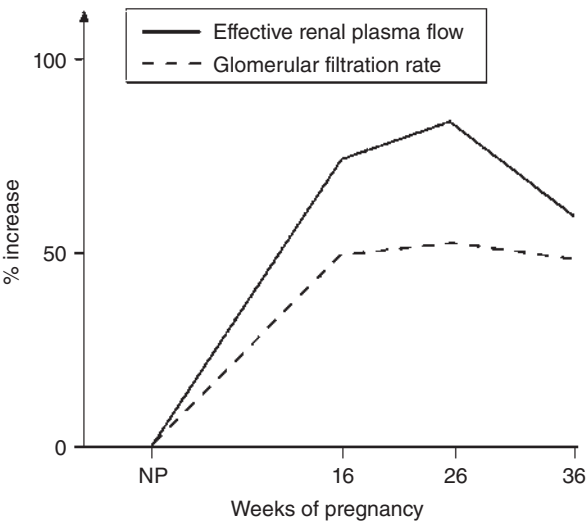
Table 1.4 Percentage changes in some coagulation and fibrinolytic variables and fibronectin levels are expressed from postpartum data in the same women. The mean values shown are those at the end of each trimester and are thus not necessarily the maxima. Note the very large rise in PAI-2 (placental type PAI) and TAT III complexes in the first trimester.

	First trimester	Second trimester	Third trimester
PAI-1 (mg/mL)	−10	+68	+183
PAI-2 (mg/mL)	+732	+1804	+6554
t-PA (mg/mL)	−24	−19	+63
Protein C (% activity)	−12	+10	+9
AT III (% activity)	−21	−14	−10
TAT III	+362	+638	+785
Fibronectin (mg/L)	+3	−12	+53

PAI, plasminogen activator inhibitor; t-PA, tissue plasminogen activator antigen; AT III, antithrombin III; TAT III, thrombin–antithrombin III complex.
Source: Halligan A, Bonnar J, Sheppard B, Darling M, Walshe J. Haemostatic, fibrinolytic and endothelial variables in normal pregnancies and pre-eclampsia. *Br J Obstet Gynaecol* 1994;101: 488–492. Oxford: Elsevier. Reproduced with permission of Elsevier.

Fig. 1.6 The changes in renal function during pregnancy are largely complete by the end of the first trimester and are thus proactive not reactive to the demands of pregnancy. The filtration fraction falls during the first trimester but begins to return to non-pregnant levels during the third trimester. *Source:* Chamberlain, G. and Broughton Pipkin, F. *Clinical Physiology in Obstetrics*, 3rd edn. Oxford: Wiley, 1998. Reproduced with permission of John Wiley & Sons.

effects on the concentrations of certain plasma metabolites and electrolytes and 'normal' laboratory reference ranges may thus be inappropriate in pregnancy. For example, plasma creatinine concentration falls significantly by the fourth week of gestation and continues to fall to mid-pregnancy, to below 50 mmol/L, but creatinine clearance begins to fall during the last couple of months of pregnancy, so plasma creatinine concentration rises again.

Total body water rises by about 20% during pregnancy (~8.5 L) with a very sharp fall in plasma osmolality between weeks 4 and 6 after conception, possibly through the actions of human chorionic gonadotrophin (hCG). The volume-sensing arginine vasopressin (AVP) release mechanisms evidently adjust as pregnancy progresses, with a lowering of the osmotic threshold for AVP and thirst. As well as water present in the fetus, amniotic fluid, placenta and maternal tissues, there is also oedema fluid and increased hydration of the connective tissue ground substance with laxity and swelling of connective tissue.

The pregnant woman accumulates some 950 mmol of sodium in the face of high circulating concentrations of progesterone, which competes with aldosterone at the distal tubule. The potentially natriuretic prostacyclin also rises markedly, with a significant rise in atrial natriuretic peptide (ANP). This stimulates the renin–angiotensin system, with increased synthesis and release of aldosterone from the first trimester. The raised plasma prolactin may also contribute to sodium retention. It is assumed that glomerulotubular balance must also change in pregnancy to allow the sodium retention that actually occurs. There is a fall of some 4–5 mmol/L in plasma sodium by term, but plasma chloride does not change. Curiously, some 350 mmol of potassium are also retained during pregnancy, in the face of the much-increased GFR, substantially raised aldosterone concentrations and a relatively alkaline urine. Renal tubular potassium reabsorption evidently adjusts appropriately to the increased filtered potassium load.

Serum uric acid concentration falls by about one-quarter in early pregnancy, with an increase in its fractional excretion secondary to a decrease in net tubular reabsorption. The kidney excretes a progressively smaller proportion of the filtered uric acid, so some rise in serum uric acid concentration during the second half of pregnancy is normal. The developing fetus and placenta contribute to the load. A similar pattern is seen in relation to urea, which is also partly reabsorbed in the nephron.

Glucose excretion may rise 10-fold as the greater filtered load exceeds the proximal tubular T_{max} for glucose (~1.6–1.9 mmol/min). If the urine of pregnant women is tested sufficiently often, glycosuria will be detected in 50%. The excretion of most amino acids increases, which is curious since these are used by the fetus to synthesize protein. The pattern of excretion is not constant, and differs between individual amino acids. Excretion of the water-soluble vitamins is also increased. The mechanism for all these is inadequate tubular reabsorption in the face of a 50% rise in GFR.

Urinary calcium excretion is also twofold to threefold higher in normal pregnancy than in the non-pregnant woman, even though tubular reabsorption is enhanced, presumably under the influence of the increased concentrations of 1,25-dihydroxyvitamin D. To counter this, intestinal absorption doubles by 24 weeks, after which it stabilizes. Renal bicarbonate reabsorption and hydrogen ion excretion appear to be unaltered during pregnancy. Although pregnant women can acidify their urine, it is usually mildly alkaline.

Total protein and albumin excretion both rise during pregnancy, to at least 36 weeks, due to the increased GFR, and changes in both glomerular and tubular function. Thus in late pregnancy, an upper limit of normal of 200 mg total protein excretion per 24-hour collection is accepted. The assessment of absolute proteinuria in pregnancy using dipsticks has been shown to give highly variable data. Studies in which urinary protein/creatinine and albumin/creatinine ratios were measured in order to identify developing pre-eclampsia have also shown marked heterogeneity in test accuracy and thus diagnosis of the disease [24].

The cerebral circulation

The brain is responsible for approximately 20% of total oxygen consumption outside pregnancy. It has a relatively limited capacity to tolerate changes in blood flow, ion or water balance, and is enclosed by a rigid container. It is thus potentially very vulnerable. Its response to the substantial changes in PV and circulating hormone concentrations, both vasoconstrictor and vasodilator, is distinct from that of other vascular beds and is geared to maintaining the status quo through autoregulation. Cerebral blood flow does appear to be unchanged during pregnancy [25].

The gastrointestinal system

Taste often alters very early in pregnancy. The whole intestinal tract has decreased motility during the first two trimesters, with increased absorption of water and salt, tending to increase constipation. Heartburn is common as a result of increased intragastric pressure. Hepatic synthesis of albumin, plasma globulin and fibrinogen increases, the latter two sufficiently to give

increased plasma concentrations despite the increase in PV. Total hepatic synthesis of globulin increases under oestrogen stimulation, so the hormone-binding globulins rise. There is decreased hepatic extraction of circulating amino acids.

The gallbladder increases in size and empties more slowly during pregnancy but the secretion of bile is unchanged. Cholestasis is almost physiological in pregnancy and may be associated with generalized pruritus but only rarely produces jaundice. However, when cholestasis of pregnancy is severe, adverse pregnancy outcomes are increasingly likely [26].

Energy requirements

The energy cost of pregnancy includes 'stored' energy in maternal and fetal tissues, and the greater energy expenditure needed for maintenance and physical activity. The weight gained during pregnancy arises from the products of conception, the increased size of maternal tissues such as the uterus and breasts, and the greater maternal fat stores. The basal metabolic rate has risen by about 5% by the end of pregnancy in a woman of normal weight [27]. The average weight gain over pregnancy in a woman of normal body mass index (BMI) is about 12.5 kg. The average weight gain from pre-pregnancy values at 6–18 months after delivery is 1–2 kg, but in about one-fifth of women can be 5 kg or more [28]. Obese women usually put on less weight during pregnancy, but retain more post partum, partly dependent on the distribution of abdominal fat before pregnancy. A 5-year follow-up of nearly 3000 women found that parous women gained 2–3 kg more than nulliparous women during this time. They also had significantly greater increases in waist/hip ratio, an independent risk factor for future cardiovascular disease [29].

Carbohydrates/insulin resistance

Pregnancy is hyperlipidaemic and glucosuric. Although neither the absorption of glucose from the gut nor the half-life of insulin seem to change and the insulin response is well maintained, by 6–12 weeks' gestation fasting plasma glucose concentrations have fallen by 0.11 mmol/L, and by the end of the first trimester the increase in blood glucose following a carbohydrate load is less than outside pregnancy [30]. This increased sensitivity stimulates glycogen synthesis and storage, deposition of fat and transport of amino acids into cells. The uptake of amino acids by the mother for gluconeogenesis may also be enhanced. After mid-pregnancy, resistance to the action of insulin develops progressively and plasma glucose concentrations rise, though remaining below non-pregnant levels (Fig. 1.7). Glucose crosses the placenta readily and the fetus uses glucose as its primary energy substrate, so this rise is presumably beneficial to the fetus. Fetal and maternal glucose concentrations are significantly correlated.

The insulin resistance is presumably largely endocrine driven, possibly via increased cortisol or human placental lactogen. Plasma leptin concentrations are directly correlated with insulin resistance during pregnancy [31] while concentrations of glucagon and the catecholamines are unaltered. Serum adiponectin, which enhances insulin sensitivity and stimulates glucose uptake in skeletal muscle, is increased in early pregnancy, falling over the second half of gestation. Adiponectin concentrations are also low in other insulin-resistant states, but whether this is cause or effect is still uncertain. High concentrations of adiponectin in early pregnancy may enhance
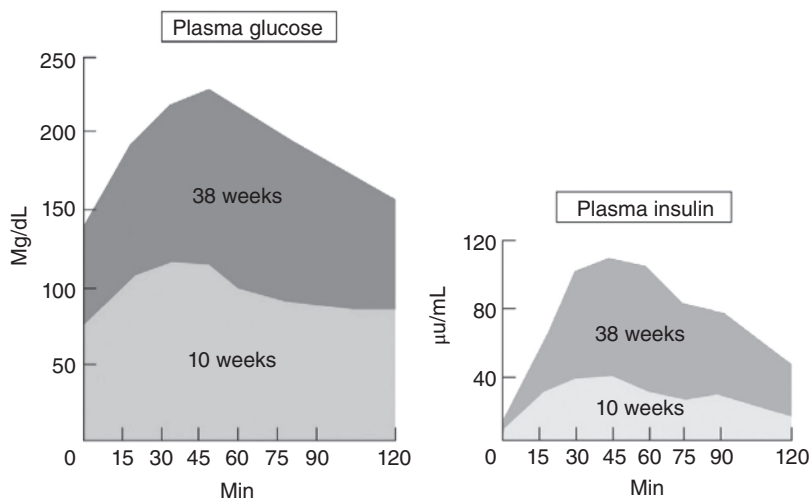

Fig. 1.7 Responses in normal pregnant women to a 50-g oral glucose load during early and late pregnancy. During early pregnancy there is a normal plasma insulin response with a relative reduction in plasma glucose concentrations compared with the non-pregnant state. In contrast, during late pregnancy plasma glucose concentrations reach higher levels after a delay despite a considerably enhanced insulin response, a pattern which could be explained by relative resistance to insulin.

maternal accumulation of nutrients, while the subsequent fall in adiponectin facilitates allocation of nutrients to the fetus. There is an inverse association between maternal serum adiponectin and fetal growth across the full range of birthweights [32].

Lipids

Serum total and low-density lipoprotein (LDL) cholesterol fall early in pregnancy, reaching their lowest levels at 6–8 weeks, but then rising to term; the early fall in AIx has been linked to the fall in LDL [11]. Conversely, high-density lipoprotein (HDL) cholesterol rises significantly by 6–8 weeks. There is a striking increase in circulating free fatty acids and complex lipids in pregnancy, with approximately threefold increases in very low density lipoprotein (VLDL) triglycerides and a 50% increase in VLDL cholesterol by 36 weeks [33], which is probably driven by oestrogens. Birthweight and placental weight are directly related to maternal VLDL triglyceride levels at term. The hyperlipidaemia of normal pregnancy is not atherogenic because the pattern of increase is not that of atherogenesis, although pregnancy can unmask pathological hyperlipidaemia.

Lipids undergo peroxidation in all tissues as part of normal cellular function. Excess production of lipid can result in oxidative stress, with damage to the cell membrane. During normal pregnancy, increases in plasma lipid peroxides appear by the second trimester in step with the general rise in lipids and may taper off later in gestation [34]. As the peroxide levels rise so do those of vitamin E and some other antioxidants; this rise is proportionately greater than that of peroxides so physiological activities are protected. Lipid peroxidation is also active in the placenta, increasing with gestation. Since the placenta contains high concentrations of unsaturated fats under conditions of low $P\text{a}O_2$, antioxidants such as vitamin A, the carotenoids and provitamin A carotenoids are required to protect both mother and fetus from free radical activity.

Early in pregnancy fat is deposited but from mid-pregnancy it is also used as a source of energy, mainly by the mother so that glucose is available for the growing fetus [35] and to provide energy stores for the high metabolic demands of late pregnancy and lactation. The accurate measurement of pregnancy-related fat deposition is technically difficult, but total accretion is estimated at about 2–6 kg. The absorption of fat from the intestine is not directly altered during pregnancy. The hormone leptin acts as a sensor, alerting the brain to the extent of body fat stores. Concentrations rise threefold during pregnancy and are directly correlated with total body fat; they are not related to the basal metabolic rate during gestation. Recent animal studies suggest that the hypothalamus, which contains the appetite-regulating centres, is desensitized to the effects of leptin in pregnancy. This allows the mother to eat more than she otherwise would consider doing, with consequent fat deposition.

Endocrine systems

The placenta is a powerhouse of hormone production from the beginning of gestation and challenges the mother's autonomy.

Placental hormones

hCG is the signal for pregnancy, but indirect effects, such as the oestrogen-driven increased hepatic synthesis of the binding globulins for thyroxine, corticosteroids and the sex steroids, also affect the mother's endocrinological function. The fetoplacental unit synthesizes very large amounts of oestrogens and progesterone, both probably being concerned with uterine growth and quiescence and with mammary gland development. However, they also stimulate synthesis of a variety of other important hormones. Oestrogens stimulate both the synthesis of the pro-angiogenic vascular endothelial growth factor (VEGF) and its tyrosine kinase receptors (see below) and angiogenesis; the two are linked. VEGF appears to interact with other placentally produced hormones and angiopoietin 2 as major players in the development of the villous capillary bed in early human pregnancy. Trophoblasts express the transmembrane tyrosine kinase receptor Flt-1 which mediates the response to VEGF-A and placental growth factor (PlGF). The soluble isoform sFlt-1 also binds VEGF-A and PlGF, but antagonizes their pro-angiogenic actions due to lack of intracellular effector regions. Levels of sFlt-1 released to the maternal circulation rise during normal pregnancy. The oxygen-sensitive transcriptional activator hypoxia-inducible factor (HIF)-1 plays a major part in the response to hypoxic conditions and is a primary regulator of angiogenesis, acting synergistically with VEGF, PlGF and the angiopoietins [36].

The peroxisome proliferator-activated receptor γ (PPARγ) is a member of the nuclear receptor superfamily and has an important role in modulating expression of numerous other genes. It is expressed in human villous and extravillous cytotrophoblast. PPARγ binds to, and is activated by, natural ligands such as eicosanoids, fatty acids and oxidized LDLs. Studies in knockout mice have shown it to be essential for placental development.

The corpus luteum, uterus and placenta synthesize relaxin, structurally very similar to insulin, during pregnancy, plasma concentrations peaking at the end of the first trimester. It is thought to regulate VEGF in very

early pregnancy and, by its effects on extracellular matrix components, stimulate uterine growth and remodelling of the spiral arteries. It may also be concerned with the systemic vascular response to pregnancy. There is wide inter-species variability, and data from animal studies should be viewed with caution [37].

The hypothalamus and pituitary gland

The pituitary gland increases in weight by 30% in first pregnancies and by 50% subsequently. The number of lactotrophs is increased and plasma prolactin begins to rise within a few days of conception and by term may be 10–20 times as high as in the non-pregnant woman; the secretion of other anterior pituitary hormones is unchanged or reduced. hCG and the gonadotrophins share a common α-subunit, and the rapidly rising hCG concentration suppresses secretion of both follicle-stimulating hormone and luteinizing hormone, thus inhibiting ovarian follicle development by a blunting of response to gonadotrophin-releasing hormone. Thyroid-stimulating hormone (TSH) secretion responds normally to hypothalamic thyrotropin-releasing hormone (also synthesized in the placenta). Adrenocorticotrophic hormone (ACTH) concentrations rise during pregnancy, partly because of placental synthesis of ACTH and of a corticotrophin-releasing hormone and do not respond to normal control mechanisms.

The adrenal gland

Both the plasma total and the unbound cortisol and other corticosteroid concentrations rise in pregnancy, from about the end of the first trimester. Concentrations of cortisol-binding globulin double. Excess glucocorticoid exposure *in utero* appears to inhibit fetal growth in both animals and humans. However, the normal placenta synthesizes a pregnancy-specific 11β-hydroxysteroid dehydrogenase, which inhibits transfer of maternal cortisol. The marked rise in secretion of the mineralocorticoid aldosterone in pregnancy has already been mentioned. Synthesis of the weaker mineralocorticoid 11-deoxycorticosterone is also increased by the eighth week of pregnancy, and actually increases proportionally more than any other cortical steroid, possibly due to placental synthesis.

The measurement of plasma catecholamines has inherent difficulties, but there is now broad consensus that plasma catecholamine concentrations fall from the first to the third trimester. There is some blunting of the rise in noradrenaline (reflecting mainly sympathetic nerve activity) seen on standing and isometric exercise in pregnancy, but the adrenaline response (predominantly adrenal) is unaltered [38].

The thyroid gland

hCG may suppress TSH in early pregnancy because they share a common α-subunit. The thyroid remains normally responsive to stimulation by TSH and suppression by triiodothyronine (T3). There is a threefold rise in the thyroid's clearance of iodine, allowing the absolute iodine uptake to remain within the non-pregnant range. Thyroid-binding globulin concentrations double during pregnancy, but other thyroid-binding proteins do not increase. Overall, free plasma T3 and thyroxine (T4) concentrations remain at the same levels as outside pregnancy (although total levels are raised), and most pregnant women are euthyroid. Free T4 may fall in late gestation [39].

Calcitonin, another thyroid hormone, rises during the first trimester, peaks in the second and falls thereafter, although the changes are not large. It may contribute to the regulation of 1,25-dihydroxyvitamin D.

The parathyroid glands and calcium metabolism

Calcium homeostasis changes markedly in pregnancy [40,41]. Maternal total plasma calcium falls because albumin concentration falls, but unbound ionized calcium is unchanged. Synthesis of 1,25-dihydroxycholecalciferol increases, promoting enhanced gastrointestinal calcium absorption. Parathyroid hormone (PTH) regulates the synthesis of 1,25-dihydroxyvitamin D in the proximal convoluted tubule. There is a fall in intact PTH during pregnancy but a doubling of 1,25-dihydroxyvitamin D; PTH-related protein (PTHrP) is also present in the maternal circulation. The main sources of PTHrP are the fetal parathyroid gland and the placenta. It is presumably placentally derived PTHrP that is transferred into the maternal circulation and affects calcium homeostasis by acting through the PTH receptor.

Renal hormones

The renin–angiotensin system is activated from very early in pregnancy (see section Cardiovascular system). A vasodilator component to the renin–angiotensin system has recently been described in which angiotensin 1–7 is the agonist; angiotensin 1–7 rises during pregnancy and may stimulate release of both nitric oxide and prostacyclin. Synthesis of erythropoietin appears to be stimulated by hCG; its concentration rises from the first trimester, peaking in mid-gestation and falling somewhat thereafter. Prostacyclin is a potent vasodilator, synthesized mainly in the renal endothelium. Concentrations begin to rise rapidly by 8–10 weeks of gestation, being

fourfold higher than non-pregnant values by the end of the first trimester.

The pancreas

The size of the islets of Langerhans and the number of β cells increase during pregnancy, as does the number of receptor sites for insulin. The functions of the pancreas in pregnancy are considered above.

The endothelium

The endothelium synthesizes a variety of hormones, both vasodilator (e.g. prostacyclin, VEGF-A, nitric oxide) and vasoconstrictor (e.g. endothelin-1). The vasodilators are mostly upregulated in pregnancy, and allow the early fall in total peripheral resistance. Interestingly, although the lipid profile in pregnancy appears to be atherogenic, endothelial function in normal pregnancy, as assessed by flow-mediated dilatation, is not impaired. This may be due to the increased estradiol concentrations, which upregulate endothelial nitric oxide synthase.

Conclusion

This chapter attempts, very briefly, to outline the physiology of normal pregnancy. The changes mostly begin very early indeed, and it may be that two of the major problems of pregnancy – intrauterine growth retardation and pre-eclampsia – are initiated even before the woman knows that she is pregnant. Better understanding of the mechanisms of very early normal pregnancy adaptation may help us to understand the abnormal.

Summary box 1.1

- Each ovulatory menstrual cycle prepares the potential mother for the physiological changes of pregnancy. Progesterone is the prime mover, and before conception initiates such changes as increased tidal volume, heart rate and GFR, as well as endometrial priming. These changes are proactive, not reactive, and in normal pregnancy are greater than physiologically necessary.
- Early pregnancy is associated with a systemic inflammatory response. The mother's immune response is altered to allow implantation and placentation and the remodelling of the spiral arteries.
- Total peripheral resistance falls very early, followed by the peripheral and central blood pressure; plasma volume and cardiac output rise. Alveolar ventilation and oxygen-carrying capacity increase more than oxygen consumption. Even normal pregnancy is associated with low-grade coagulopathy.
- Renal filtration increases very early. The rise in filtered sodium load activates the renin–angiotensin system, allowing sodium retention and the increased plasma volume. Plasma concentrations of various analytes are reduced because of both increased filtration and plasma volume expansion. Aminoaciduria and glycosuria are common.
- The average weight gain over pregnancy in a woman of normal BMI is about 12.5 kg. Some of this is usually retained after delivery. Pregnancy is associated with insulin resistance and hyperlipidaemia; there is considerable fat deposition.
- The placenta is a powerhouse of hormone and cytokine synthesis, modifying the mother's physiology for the demands of pregnancy.

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