Dewhurst’s Textbook of Obstetrics & Gynaecology
This book is dedicated to my wife, Gill, and my children, Alastair, Nicholas and Timothy, and to the memory of Sir Jack Dewhurst.
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Professor Sir John Dewhurst died on 1 December 2006. Jack, as he was known to all his colleagues, was a doyen amongst obstetricians and gynaecologists of the twentieth century. His reputation was internationally renowned and he became a worldwide expert in paediatric and adolescent gynaecology, for which he received due accolade. He was also an outstanding teacher of obstetrics and gynaecology, and, as such, this textbook, which he began in the 1970s, is testament to his dedication to the passing on of knowledge to others. In 1976 he became President of the Royal College of Obstetricians and Gynaecologists, a post he held for 3 years, for which he was subsequently knighted. He retired in 1986 after a long and distinguished career, but his legacy lives on and he will be remembered with great affection and professional respect by all who knew him.

Keith Edmonds
December 2011
As I write this, it is almost 40 years since the 1st edition of Dewhurst’s Postgraduate Obstetrics and Gynaecology was published. There are only a very few books that have stood the test of such longevity and it is a tribute to the concept that Jack Dewhurst had that the book continues now into its 8th edition. Jack’s concept was to provide the postgraduate student with an advanced and integrated text for education and it is that philosophy which carries into this, the 8th, edition. No textbook can be totally comprehensive, and any postgraduate student reading this text we hope will be stimulated by the knowledge gained to go on and acquire further, more in-depth and specialist knowledge.

This edition has been redesigned with the hope that the readers will acquire knowledge in as quick and as comprehensive a way as possible. The specialty continues to develop and advance and gynaecology particularly is becoming increasingly a medical specialty and less of a surgical one. This of course is to the benefit of women as therapeutic advances offer them an increasing range of options to improve their quality of life. Obstetrics becomes increasingly focused on differentiating between the normal and the complicated pregnancy, with increasing emphasis on improved treatments for medically compromised mothers and fetuses and subsequently neonates. Again, quality of life is the overriding tenet as the practice of obstetrics and gynaecology improves worldwide.

It is still extremely sad that a quarter of a million women die every year worldwide as a result of childbirth and it is hoped that this volume will make some contribution towards improving these figures.

Many new authors have accepted the challenge to contribute to this edition and, along with those authors who have contributed in the past, I offer my sincere thanks for the time and effort they have put into constructing their chapters. We hope we have done this in a way that the reader will find intellectually challenging and rewarding.

Finally, I would like to thank my secretary, Liz Manson, who has been the tower of strength behind the production of this volume, and also the team at Blackwell Publishing, which has changed several times during the nidation of this edition but has never wavered in their endeavour to achieve the final vision.

Keith Edmonds
December 2011
Our purpose in writing this book has been to produce a comprehensive account of what the specialist in training in obstetrics and gynaecology must know. Unfortunately for him, he must now know a great deal, not only about his own subject, but about certain aspects of closely allied specialties such as endocrinology, biochemistry, cytogenetics, psychiatry, etc. Accordingly we have tried to offer the postgraduate student not only an advanced textbook in obstetrics and gynaecology but one which integrates the relevant aspects of other subjects which nowadays impinge more and more on the clinical field.

To achieve this aim within, we hope, a reasonable compass we have assumed some basic knowledge which the reader will have assimilated throughout his medical training, and we have taken matters on from there. Fundamental facts not in question are stated as briefly as is compatible with accuracy and clarity, and discussion is then devoted to more advanced aspects. We acknowledge that it is not possible even in this way to provide all the detail some readers may wish, so an appropriate bibliography is provided with each chapter. Wherever possible we have tried to give a positive opinion and our reasons for holding it, but to discuss nonetheless other important views; this we believe to be more helpful than a complete account of all possible opinions which may be held. We have chosen moreover to lay emphasis on fundamental aspects of the natural and the disease processes which are discussed; we believe concentration on these basic physiological and pathological features to be important to the proper training of a specialist. Clinical matters are, of course, dealt with in detail too, whenever theoretical discussion of them is rewarding. There are, however, some clinical aspects which cannot, at specialist level, be considered in theory with real benefit; examples of these are how to palpate a pregnant woman’s abdomen and how to apply obstetric forceps. In general these matters are considered very briefly or perhaps not at all; this is not a book on how things are done, but on how correct treatment is chosen, what advantages one choice has over another, what complications are to be expected, etc. Practical matters, we believe, are better learnt in practice and with occasional reference to specialized textbooks devoted solely to them.

A word may be helpful about the manner in which the book is set out. We would willingly have followed the advice given to Alice when about to testify at the trial of the Knave of Hearts in Wonderland, ‘Begin at the beginning, keep on until you come to the end and then stop’. But this advice is difficult to follow when attempting to find the beginning of complex subjects such as those to which this book is devoted. Does the beginning lie with fertilization; or with the events which lead up to it; or with the genital organs upon the correct function of which any pregnancy must depend; or does it lie somewhere else? And which direction must we follow then? The disorders of reproduction do not lie in a separate compartment from genital tract disease, but each is clearly associated with the other for at least part of a woman’s life. Although we have attempted to integrate obstetrics with gynaecology and with their associated specialties, some separation is essential in writing about them, and the plan we have followed is broadly this – we begin with the female child in utero, follow her through childhood to puberty, through adolescence to maturity, through pregnancy to motherhood, through her reproductive years to the climacteric and into old age. Some events have had to be taken out of order, however, although reiteration has been avoided by indicating to the reader where in the book are to be found other sections dealing with different aspects of any subject under consideration. We hope that our efforts will provide a coherent, integrated account of the field we have attempted to cover which will be to the satisfaction of our readers.

Sir John Dewhurst
1972
Section 1

Obstetrics
Part 1

Basic Science
Chapter 1
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 [1]. Most pregnancy-driven changes are qualitatively in place by the end of the first trimester, only maturing in magnitude thereafter. 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 the 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.

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 [5]. The outer 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 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, but include locally-generated nitric oxide, probably acting through cyclic GMP or voltage-gated potassium channels, while a number of hormones such as prostacyclin, prostaglandin (PG)E2 and calcitonin gene-related peptide act through G_{i} receptors, and are relaxatory.

**The cardiovascular system**

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 the plasma volume (PV) (Fig. 1.1) [6,7]. 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 [8]. 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.

Measuring systemic arterial blood pressure in pregnancy is notoriously difficult, but there is now broad consensus that Korotkoff 5 should be used with auscultatory techniques [9]. However measured, there is a small fall in systolic, and a greater fall in diastolic, blood pressure during the first half of pregnancy, 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.

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.
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.

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

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.

Source: data from Robson et al. [8].

**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) [10]. Neither forced expiratory volume in 1s (FEV₁) 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 $P_{CO₂}$ is lowest in early gestation. Progesterone also increases erythrocyte carbonic anhydrase concentration, which will also lower $P_{CO₂}$. Carbon dioxide production rises sharply during the third trimester, as fetal metabolism increases. The fall in maternal $P_{CO₂}$ allows more efficient placental transfer of carbon dioxide from the fetus, which has a $P_{CO₂}$ of around 55 mmHg (7.3 kPa). The fall in $P_{CO₂}$ results in a fall in plasma bicarbonate concentration (to about 18–22 mmol/L compared with the normal of 24–28 mmol/L), which contributes to the fall in plasma osmolality; 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 $P_{O₂}$ 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. This facilitates oxygen unloading to the fetus, which has both a much lower $P_{O₂}$ (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 of the blood (see section Haematology) is about 18%, there is
8 Chapter 1

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 β1-globulin, transferrin. 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 15µg/L, indicative of low iron stores [12]; a similar survey appears not to have been undertaken since then (UK Scientific Advisory Committee on Nutrition Report 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 [11]. This is shown in the response to moderate exercise (Table 1.3).

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**Table 1.2** The influence of pregnancy on some respiratory variables.

<table>
<thead>
<tr>
<th></th>
<th>Non-pregnant</th>
<th>Pregnant – term</th>
</tr>
</thead>
<tbody>
<tr>
<td>PO2 (mmHg)</td>
<td>93 (12.5kPa)</td>
<td>102 (13.6kPa)</td>
</tr>
<tr>
<td>O2 consumption (mL/min)</td>
<td>200</td>
<td>250</td>
</tr>
<tr>
<td>PCO2 (mmHg)</td>
<td>35–40 (4.7–5.3kPa)</td>
<td>30 (4.0kPa)</td>
</tr>
<tr>
<td>Venous pH</td>
<td>7.35</td>
<td>7.38</td>
</tr>
</tbody>
</table>

**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.

<table>
<thead>
<tr>
<th></th>
<th>Resting</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output</td>
<td>+33% (4.5–6 L/min)</td>
<td>+167% (up to 12 L/min)</td>
</tr>
<tr>
<td>Minute ventilation</td>
<td>+40% (7.5–10.5 L/min)</td>
<td>+1000% (up to ∼80 L/min)</td>
</tr>
</tbody>
</table>

---

**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.

**Fig. 1.4** Flow chart of the effects of over-breathing. HCO3−, bicarbonate; Na+, sodium; PCO2, carbon dioxide tension; PROG, progesterone.

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**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 β1-globulin, transferrin. 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 15µg/L, indicative of low iron stores [12]; a similar survey appears not to have been undertaken since then (UK Scientific Advisory Committee on Nutrition Report
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) [13]. 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 plasma volume 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, -E and -G) expressed by the invasive cytotrophoblasts. This is likely to be central to the maternal recognition of the conceptus [14] (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
Continuing low-grade coagulopathy is a feature of normal pregnancy [15]. Several of the potent procoagulatory factors rise from at least the end of the first trimester (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 the 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.

**Table 1.4** Percentage changes in some coagulation (upper) 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.

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

PAI, plasminogen activator inhibitor; t-PA, tissue plasminogen activator antigen; AT III, antithrombin III; TAT III, thrombin–antithrombin III complex.
Source: Data from Halligan et al. [16].
return to non-pregnant levels during the third trimester. The filtration fraction falls during the first trimester but begins to stabilize thereafter. However, these major increments do not keep up (e.g. glucose and amino acids; see below).

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 [17]. 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 renal prostacyclin 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 towards non-pregnant values thereafter. 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 below). These changes have profound 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 release mechanisms evidently adjust as pregnancy progresses. 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 small 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. 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 \( T_{\text{max}} \) 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 proteinuria in pregnancy using dipsticks has been shown to give highly variable data.

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.

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 [18]. The average weight gain over pregnancy in a woman of normal weight is 11 kg or more [19]. Obese women usually put on less weight during pregnancy, but retain more post partum. 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 [20].

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 [21]. 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 [22] while concentrations of glucagon and the catecholamines are unaltered. Adiponectin concentrations fall in pregnancy and are negatively correlated with fasting insulin concentrations and white fat mass. Adiponectin concentrations are also low in other insulin-resistant states, but whether this is cause or effect is still uncertain.

Lipids

Total plasma cholesterol falls early in pregnancy, reaching its lowest point at 6–8 weeks, but then rises to term. There is a striking increase in circulating free fatty acids and complex lipids in pregnancy, with approximately three-fold increases in very low density lipoprotein (VLDL) triglycerides and a 50% increase in VLDL cholesterol by 36 weeks [23], which is probably driven by oestrogens. High-density lipoprotein (HDL) cholesterol is also increased. 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 [24]. 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 [25] 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 vascular endothelial growth factor (VEGF) and its tyrosine kinase receptors and angiogenesis; the two are linked. VEGF appears to interact with other placently produced hormones and angiopoietin-2 as major players in the development of the villous capillary bed in early human pregnancy. 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 low-density lipoproteins. Studies in knockout mice have shown it to be essential for placental development.

**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 $\alpha$-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.