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ESSENTIALS Almost every maternal organ system makes a physiological adapta- tion to pregnancy for optimal pregnancy outcome. An understanding of these adaptations brings insight into the aetiology of gestational syndromes and helps the clinician to manage pregnant women with pre-existing chronic illness. Physiological adaptations in pregnancy include: (1) cardiovas-cular—cardiac output increases by 30–40%; (2) respiratory—oxygen consumption increases 20%; and (3) renal—glomerular filtration rate increases 55%. Biochemical and endocrine changes in pregnancy include: altered normal ranges for many important metabolic and endocrine labora- tory tests, such as (1) serum creatinine and urea—both decreased; (2) cholesterol and triglycerides—both increased; (3) liver blood tests—alkaline phosphatase increased up to fourfold; and (4) thy- roid function tests—free thyroxine and tri-iodothyronine levels fall, thyroid-stimulating hormone levels fall then rise. Awareness of these changes is essential, both for recognition of disease in pregnancy and to prevent inappropriate pursuit of test results that are normal in pregnancy. Long-term implications of pregnancy syndromes: pre-eclampsia and gestational diabetes mellitus for example, can be considered ex- aggerated responses to pregnancy that resolve after childbirth, but herald hypertension and diabetes mellitus in later life. Introduction Pregnancy makes extra physiological demands on almost all ma- ternal organs. Women with pre-pregnancy disease may be unable to meet these gestational demands, which puts their own health at risk and compromises pregnancy outcome. In some women, the physio- logical changes of pregnancy unmask a subclinical predisposition to future disease through the transient development of gestational syndromes, such as pre-eclampsia and gestational diabetes mellitus. In this respect pregnancy acts as a maternal ‘stress test’ that identifies a woman’s vulnerability to future disease. An understanding of the normal physiological demands of pregnancy not only brings insight into the aetiology and management of gestational syndromes, but also helps the clinician advise women with pre-existing chronic illness about the risks and consequences of pregnancy. Preparing for pregnancy The female body prepares for pregnancy during every menstrual cycle. It is not only the endometrium that anticipates implantation of a fertilized ovum, but the whole cardiovascular system. During the postovulatory or luteal phase of each menstrual cycle there is a de- crease in systemic vascular resistance by approximately 20%, leading to a 10% fall in mean arterial pressure

compared with the follicular phase. Cardiac output increases by almost 20%, and renal vasodilatation increases both renal blood flow and glomerular filtration by approximately 10%. All of these changes resolve with involution of the corpus luteum and onset of menses. Cardiovascular changes in pregnancy If fertilization is successful, the haemodynamic changes established in the menstrual cycle progress further. Systemic vascular resistance (SVR) falls by almost 40% and causes a maximal decrease in mean arterial pressure by mid-pregnancy. Both systolic and diastolic blood pressure fall significantly by week 5–6 of healthy pregnancy, then rise to nonpregnancy levels at term. In normal weight, nulliparous women having a normal pregnancy, the mean blood pressure (95% reference range) at 12 weeks is 112/65 (89–136/49–82) mm Hg and at 37 weeks 116/70 (92–140/52–88) mm Hg. Heart rate increases by approximately 20%, from a pre-pregnancy average 72 beats/min (range 60–100 bpm) to 85 beats/min at term (range 72–120). The rise in stroke volume and fall in SVR results in a 30–40% increase in cardiac output by 24 weeks, which is sustained until the final weeks of pregnancy. During the third trimester, cardiac output falls in the supine position when the gravid uterus compresses the inferior vena cava. Throughout pregnancy, left ventricular wall thickness and left ventricular mass increase by up to 30% and 50%, respectively. Cardiac output returns almost completely to pre-pregnancy levels within two weeks of delivery. 14.1 Physiological changes of normal pregnancy David J. Williams

Section 14 Medical disorders in pregnancy 2564 Distribution of increased cardiac output Although it is technically difficult to measure blood flow to par- ticular maternal viscera during pregnancy, it is clear that the timing and extent of changes to blood flow varies between organs. This is summarized in Fig. 14.1.1. Mammary artery blood flow increases early in pregnancy and causes breast tenderness and swelling. Mechanism of gestational cardiovascular change As blood flow to maternal visceral organs increases during the menstrual cycle, maternal rather than fetoplacental factors are implicated in the early cardiovascular adaptations to pregnancy. Oestrogen, mainly in the form of 17β-oestradiol and the 6 KDa hormone relaxin, are potent vasodilators. Both are produced by the corpus luteum during the luteal phase of each menstrual cycle and for the first 10 weeks of pregnancy. After 10 weeks, the pla- centa secretes its own 17β-oestradiol, so that by 37 weeks' gestation maternal oestradiol levels are approximately 250-fold higher than those found during the menstrual cycle. 17β-Oestradiol relaxes vascular smooth muscle through both endothelium-dependent and independent mechanisms, and all of the endothelium-derived vasodilators—nitric oxide, prostacyclin, and endothelial-derived hyperpolarizing factor—have been implicated in the gestational fall of systemic vascular resistance. Relaxin has both rapid and sustained vasodilatory effects that work through activation of endo- thelial nitric oxide synthase, and vascular endothelial and placental growth factors, respectively. Much less is known about the vascular effects of progesterone, whose circulating levels increase by a similar amount to 17β-oestradiol and may play a role in reducing pressor responsiveness to angiotensin II. Although the precise mechanism of maternal vasodilatation is likely to be different in different vascular beds, a healthy endothe- lium is essential for normal cardiovascular adaptation to pregnancy. Fluid balance during pregnancy Arterial dilatation creates a relatively underfilled state, which stimu- lates the renin–angiotensin–aldosterone system. As a result, sodium and water retention throughout pregnancy leads to a 6–8 litre rise Fig. 14.1.1 Changes in maternal organ blood flow during healthy pregnancy. DBP, diastolic blood pressure; ERPF, estimated renal plasma flow; GFR, glomerular filtration rate; SBP, systolic blood pressure.

14.1 Physiological changes of normal pregnancy 2565 in total extracellular fluid volume. Plasma volume increases steadily until week 32, when it is 40% (or c.1.2 litres) above nonpregnant levels. This is partly mediated by a fall in the osmotic threshold for thirst, with a concomitant fall in the threshold for secretion of anti- diuretic hormone (AVP) preventing a water diuresis and sustaining a lower plasma osmolality by 10 mosmol/kg until term. During the second half of pregnancy, placental production of vasopressinase in- creases maternal AVP degradation, but plasma AVP levels remain stable as pituitary secretion of AVP normally increases fourfold. A failure of increased maternal AVP secretion leads to transient diabetes insipidus of pregnancy. Plasma atrial natriuretic pep- tide levels are normal until the second trimester, when they rise by approximately 40%. Immunological changes during pregnancy It is often presumed that pregnant women are immunosuppressed in order not to reject the fetal semi-allograft. This is not true. Certain aspects of maternal immunity are modulated, but it is the placenta that deserves most credit for eluding maternal immunity. Much harm is prevented by the physical separation of maternal and fetal blood. For instance, when this placental barrier is breached a rhesus- negative mother can be exposed to rhesus-positive fetal blood and then develop alloantibodies that will haemolyse red cells of future rhesus-positive offspring. In normal pregnancy the placenta must invade uterine tissue, the decidua. To avoid a hostile immune response the surface layers of placenta, extravillous trophoblast, express both a unique non- polymorphic HLA G and a classical polymorphic histocompati- bility antigen, HLA C. The unique interaction between placental HLA C subgroup and maternal decidual natural killer (NK) cell immunoglobulin receptor appears to dictate the level of placental invasion and consequent pregnancy success. The placenta also ex- presses a plethora of complement control systems to protect itself from the gestational rise in serum levels of maternal complement factors C3 and C4. Innate immunity is modulated in pregnancy so that maternal NK cell activity at the uteroplacental interface promotes placental in- vasion, but intercurrent infection can activate latent NK cytolytic activity to harm fetal and maternal tissues. Fetal survival is also enhanced by a shift away from maternal T-helper 1 cytokine re- sponses, which promote cell-mediated immunity towards a stronger T-helper 2 cytokine response that promotes antibody production. In consequence, pregnant women are more prone to severe infec- tions with intracellular pathogens such as malaria, tuberculosis, listeria, and Salmonella typhimurium, and they are also more likely to suffer reactivation of viruses such as Epstein–Barr. However, T regulatory cells are elevated in healthy pregnancy and may also reduce autoimmune and alloimmune responses to maternal self and fetoplacental antigens. Circulating levels of maternal immunoglobulin increase and im- munoglobulin heavy chain (IgG) transferred across the placenta provides passive immunity to the fetus. Neutrophils increase in number and develop a proinflammatory phenotype. Mean total white cell count increases to 9.0 × 109/litre and can rise as high as 40.0 × 109/litre during labour, returning to normal within six days. Erythrocyte sedimentation rate (ESR) rises as a consequence of in- creased fibrinogen and globulin: an ESR over 30 mm/h is usual, and up to 70 mm/h is within normal limits. Circulating levels of C-reactive protein do not change during healthy pregnancy and remain a good marker of incidental inflammation. Anatomical changes to the maternal immune system include involution of the thymus and enlargement of the spleen. Understanding gestational immune modulation and how it fails in pathological pregnancies will facilitate measures to improve preg- nancy outcome. Ventilatory changes during pregnancy The increased metabolic demands of pregnancy lead to a pro- gressive increase in oxygen consumption of up to almost 20% by term. Pregnant women breathe more deeply, but not more quickly, to achieve this. Tidal volume increases from approximately 500 to 700 ml, and effective alveolar ventilation actually surpasses the body’s

demand for oxygen, creating a respiratory alkalosis with Pco2 falling from 5.0 to 4.0 kPa. Progesterone stimulates deeper breathing by a direct effect on the respiratory centre, particularly increasing sensitivity to CO2. Renal changes during pregnancy By 16 weeks gestation, renal blood flow has increased by 80% (Fig. 14.1.1) and glomerular filtration rate by 55%. The rise in renal blood flow causes the kidneys to swell so that they appear approximately 1 cm longer on ultrasonography. The renal pelvis and ureters dilate, sometimes appearing obstructed to those unaware of these changes. Serum levels of creatinine and urea fall, so that levels considered normal outside pregnancy may reflect renal impairment during pregnancy. Proteinuria increases during pregnancy, but levels above 300 mg/24 h, or a protein:creatinine ratio greater than 30 mg/mmol should be considered abnormal. Gestational glycosuria reflects re- duced tubular glucose reabsorption and does not necessarily indi- cate hyperglycaemia. Furthermore, reduced tubular absorption of bicarbonate creates a metabolic acidosis that compensates for the respiratory alkalosis, keeping maternal pH at 7.4. The renal production of erythropoietin, active vitamin D, and renin increases during healthy pregnancy, but their effects are masked by other physiological changes. In early pregnancy, per- ipheral vasodilatation exceeds the renin–aldosterone mediated plasma volume expansion, hence mean arterial pressure falls until the third trimester. The 40% expansion of plasma volume exceeds the effect of a two to fourfold increase in maternal serum erythro- poietin levels, which stimulates only a 25% rise in red cell mass. This creates a ‘physiological anaemia’, which should not normally cause haemoglobin concentration to fall to less than 98 g/litre (see Chapter 14.17). Similarly, active vitamin D circulates at twice nongravid levels, but concomitant halving of parathyroid hormone levels, as well as hypercalciuria and increased fetal requirements, keeps plasma ionized calcium levels unchanged.

Section 14 Medical disorders in pregnancy 2566 Liver metabolism during pregnancy Hepatic artery and portal vein blood flow increase during the third trimester of healthy pregnancy (Fig. 14.1.1). Hepatic syn- thetic function and metabolism lead to an increase in serum concentrations of fibrinogen, ceruloplasmin, transferrin, and binding proteins such as thyroid-binding globulin, but a fall in serum albumin levels by approximately 25%. At term, serum cholesterol is raised by 50% and triglycerides by up to 300%. Increasing demands for maternal energy production are met through increased activity of the tricarboxylic acid cycle and ketogenesis during the third trimester. The normal ranges for aspartate transaminase, alanine transaminase, γ-glutamyl trans- ferase, and bilirubin decrease by as much as 20% from the first trimester until term. Maternal serum bile acid levels remain un- changed throughout healthy pregnancy (third trimester mean and 95% CI; 3.9 µmol/litre (1.8–8.2 µmol/litre)). After 20 weeks’ gestation, placental production of alkaline phosphatase increases maternal plasma levels by up to fourfold. Telangiectasia and palmar erythema are common signs of healthy pregnancy that resolve postpartum. The gastrointestinal system in pregnancy Nausea and vomiting affect about 60% of women during the first trimester. The rise and fall of hCG levels correlate temporally with the onset and improvement of these symptoms, but the underlying cause is undoubtedly multifactorial. Relaxation of intestinal smooth muscle by progesterone and relaxin creates many of the other pregnancy-induced gastrointestinal changes: gastric motility and small-bowel transit are slowed, especially during labour; the gallbladder enlarges and empties slowly in response to meals; a de- crease in lower oesophageal pressure leads to gastro-oesophageal re- flux in many women. Endocrine changes in pregnancy Thyroid function The thyroid faces three challenges during pregnancy. First, increased renal clearance of iodide and losses to the fetus create a state of rela- tive iodine deficiency. Pregnancy therefore stimulates growth of thy- roid goitres, particularly when dietary iodine intake is low.

Secondly, high oestrogen levels induce hepatic synthesis of thyroid-binding globulin, but free thyroxine (T4) and tri-iodothyronine (T3) levels fall progressively during pregnancy to levels below the normal range for nonpregnant women (Table 14.1.1). Thirdly, placental hCG shares structural similarities with thyroid-stimulating hormone (TSH) and has weak TSH-like activity. For this reason, TSH levels fall in the first trimester, but rise back towards nonpregnancy levels in the third - trimester (Table 14.1.1). Although hCG rarely stimu- lates free T4 levels into the thyrotoxic range, trophoblastic disease and hyperemesis gravidarum associated with high hCG levels can lead to biochemical hyperthyroxinaemia and suppression of TSH suggestive of thyrotoxicosis. Importantly, under these circum- stances the mother remains clinically euthyroid and her thyroid bio- chemistry will resolve with resolution of hyperemesis. Pituitary function The maternal pituitary makes only a small contribution to a suc- cessful pregnancy once ovulation has occurred and the uterus is prepared for implantation. The only pituitary hormone to in- crease significantly during pregnancy (by c.10-fold) is prolactin, which is responsible for breast development and subsequent milk production. Pituitary secretion of growth hormone (GH) is mildly suppressed during the second half of pregnancy by placental production of a GH variant, the role of which is unclear, but it may contribute to ges- tational insulin resistance. Placental production of adrenocorticotropic hormone (ACTH) leads to an increase in maternal ACTH levels, but not beyond the normal range for nonpregnant subjects. Free cortisol levels double, and in the second half of pregnancy may contribute to insulin resist- ance and striae gravidarum. High oestrogen levels during pregnancy stimulate lactotroph hyperplasia and result in pituitary enlargement. These high levels, together with those of progesterone, suppress luteinizing hormone (LH) and follicular stimulating hormone (FSH). Plasma follicular stimulating hormone levels recover within two weeks of child- birth, but pulsatile luteinizing hormone release is generally not Table 14.1.1 Important gestational changes during pregnancy Nonpregnant First trimester Second trimester Third trimester Haemoglobin (g/dl) 109–151 110–143 100–137 98–137 Platelets (×109/litre) 168–433 174–391 171–409 155–429 White cell count (×109/litre) 4.3–12.4 5.7–13.6 6.2–14.8 5.9–16.9 Alanine transaminase (IU/litre) 0–40 6–32 6–32 6–32 Serum creatinine (μmol/litre) 73 ± 10 60 ± 8 54 ± 10 64 ± 9 Plasma urea (mmol/litre) 4.3 ± 0.8 3.5 ± 0.7 3.3 ± 0.8 3.1 ± 0.7 Plasma urea (μmol/litre) 246 ± 59 189 ± 48 214 ± 71 269 ± 56 Thyroid function free T4 (pmol/litre) TSH (mlU/litre) 12.0–22 0.25–4.2 11.1–18.5 0.02–3.12 9.8–16.3 0.34–2.99 8.6–14.6 0.38–5.43 Fasting cholesterol (mmol/litre) 5.0 ± 0.3 5.5 ± 0.4 6.9 ± 0.4 7.8 ± 0.4

 resumed until after breastfeeding. Elevated prolactin levels inhibit gonadotropin-releasing hormone (GnRH) and hence luteinizing hormone in breastfeeding mothers. Carbohydrate metabolism Women develop insulin sensitivity during the first half of preg- nancy, but insulin resistance after 20 weeks' gestation. In the second half of pregnancy a glucose load will stimulate greater maternal insulin release, but with less effect. Obese women who are already insulin resistant are more likely to develop gestational diabetes mellitus. Hormones that might mediate this insulin re- sistance include cortisol, progesterone, oestrogen, and human placental lactogen. Placental production of human placental lactogen, a GH-like protein, coincides temporally with insulin resistance. Coagulation In anticipation of haemorrhage at childbirth, normal pregnancy is characterized by low-grade, chronic intravascular coagulation within both the maternal and uteroplacental circulation. During pregnancy maternal levels of clotting factors V, VIII, and X increase, while anticoagulant factors decrease; particularly protein S levels and fibrinolytic activity. These changes lead to an acquired protein C resistance in nearly half of all pregnant women. However, physio- logical contraction of the uterus by oxytocin at

childbirth is the most effective way to prevent peripartum haemorrhage. Skin and hair during pregnancy Hyperpigmentation affects up to 90% of pregnant women. Areas that are normally hyperpigmented, such as the areolae and vulva, become darker. This may be mediated by oestrogen and progesterone, which are powerful melanogenic stimulants. Hair growth increases during pregnancy and hair loss is accelerated postpartum. The gestational rise in corticosteroids and ovarian androgens contributes to the number of hairs in the growing phase (anagen). The levels of these hormones fall postpartum and hair growth moves back into the resting phase (telogen). FURTHER READING Chapman AB, et al. (1998). Temporal relationships between hormonal and hemodynamic changes in early human pregnancy. Kidney Internat, 54, 2056–63. Conrad KP (2011). Maternal vasodilatation in pregnancy: the emerging role of relaxin. Am J Physiol Regul Integr Comp Physiol, 301, R267–75. Kenyon A, Adamason AP, Williams DJ (2010). Physiology. In: Bennett P, Williamson C (eds) Basic science in obstetrics and gynaecology, 4th edition, Chapter 10. Churchill Livingston, London. Macdonald-Wallis C, et al. (2015). Gestational-age-specific reference ranges for blood pressure in pregnancy: findings from a prospective cohort. J Hypertens, 33, 96–105. McNeil AR, Stanford PE (2015). Reporting thyroid function tests in pregnancy. Clin Biochem Rev, 36, 109–26. Poppas A, et al. (1997). Serial assessment of the cardiovascular system in normal pregnancy. Circulation, 95, 2407–15. Williams DJ (ed) (2015). Maternal medicine. Preface: issue 29.5. Best Pract Res Clin Obstet Gynaecol, 29, 577–8.

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