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Edited by Alexander Heazell, Errol R. Norwitz, Louise C. Kenny and Philip N. Baker

Excerpt

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Adaptations of maternal cardiovascular and renal physiology to pregnancy

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Fergus P. McCarthy and Louise C. Kenny

■ Introduction

Major cardiovascular and renal changes occur during pregnancy to ensure optimal development of the placenta and fetus, and to protect the health of the mother. These changes include increases in the cardiac output and reductions in the systemic vascular resistance and systemic blood pressure. A clear understanding of all these changes is necessary in order to understand how disruptions in the normal physiological responses to pregnancy result in pathological conditions associated with pregnancy such as pregnancy-induced hypertension and preeclampsia.

■ Physiological hematological changes in pregnancy

To understand the cardiovascular changes which occur during pregnancy it is important to consider first of all the hematological changes that occur, as these will have an important influence on the changes which are required in pregnancy by the cardiovascular system.

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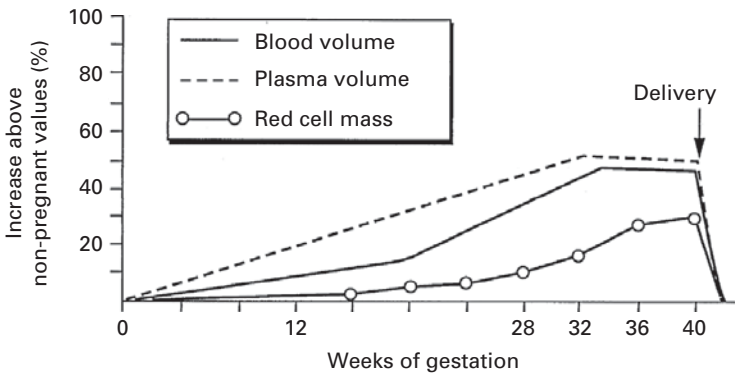


Figure 1.1 Increase in blood volume and its components in pregnancy.

Blood volume

In pregnancy, plasma volume increases by over a litre from 2600 mL to approximately 5000 mL. This occurs early in pregnancy and plateaus by approximately 32 weeks’ gestation (Figure 1.1). This increase in plasma volume is approximate and correlates with the size of the fetus. Multiple pregnancies therefore are associated with a greater increase in plasma volume while pregnancies where the fetus is growth restricted are associated with a suboptimal increase in plasma volume. The blood volume in pregnant women at term is approximately 100 mL/kg [1].

Hematological indices

The red cell mass increases in a linear fashion by approximately 30% throughout pregnancy (Figure 1.1), from a non-pregnant level of 1400 mL to approximately 1700 mL [2]. The increase in cell mass is stimulated by increased erythropoietin synthesis and varies depending on the use of iron supplementation [3]. Plasma volume increases proportionately more than red cell mass and therefore the hematocrit and hemoglobin concentrations fall during pregnancy resulting in a physiological anemia. This physiological anemia becomes most apparent at 30–34 weeks when plasma volume peaks in relation to red cell volume. Although significant clinical effort is directed at reducing this physiological anemia, this and the hypervolemia that occurs in pregnancy are not without benefit. In fact, the absence of this physiological anemia is associated with a

higher incidence of adverse pregnancy outcomes [4]. Physiological anemia and hypervolemia result in a decreased blood viscosity which in turn results in reduced resistance to flow therefore improving placenta perfusion and lowering cardiac workload. The term physiological anemia is misleading, as by the time the mother reaches full term, maternal blood volume has increased by approximately 50% above non-pregnant levels and the woman has a greater total hemoglobin than when non-pregnant to allow for any blood loss associated with delivery. Following delivery, placental separation, and uterine contractions approximately 500 mL of blood is transferred back to the maternal circulation from the uteroplacental unit to minimize any circulatory deficits which may result from blood loss at delivery. During pregnancy, iron is removed from the iron stores held in the bone marrow, the liver, and the spleen for use by the mother, and transferred to the fetus. This decrease in the quantity of stored iron is reflected in decreased serum ferritin levels.

In addition to changes in the red cell mass, there is also an increase in the white cell count and platelet count. The increase in white cell count is mainly due to an increase in neutrophil polymorphonuclear leukocytes and reaches its peak at 30 weeks' gestation. During labor there is a fourfold increase in the number of neutrophils but a fall in the number of eosinophils. During pregnancy lymphocyte function and cell-mediated immunity are profoundly suppressed resulting in a lowered resistance to viral infection.

The mean platelet count remains normal or decreases slightly in normal pregnancy, but platelet function does not appear to be altered. The serum protein pattern alters with total protein, albumin, and gamma globulin falling in the first quarter and then rising slowly towards term. Total protein concentration falls from approximately 70 g/L to 60 g/L with the decrease mainly due to a fall in albumin levels. Beta globulin and the fibrinogen factors rise causing a fourfold increase in the erythrocyte sedimentation rate (ESR) rendering this laboratory test difficult to interpret in pregnancy.

Coagulation factors

Pregnancy is a prothrombotic state and the majority of clotting factors either remain constant or increase during pregnancy. During the third trimester, plasma levels of von Willebrand factor are elevated promoting platelet aggregation and coagulation. Fibrinogen levels (factor I) increase

significantly, in addition to factors II, V, VII, VIII, X, and XII. Protein S, an endogenous anticoagulant is reduced and there is an increase in the resistance to activated protein C. Endothelium production of the fibrinolytic inhibitors plasminogen activator inhibitor-1 (PAI-1) and PAI-2 increases, in addition to tissue plasminogen activator (t-PA). The net result of these changes are both inhibition and promotion of fibrinolysis respectively. Overall there is a 20% reduction in the prothrombin and the partial thromboplastin times.

■ Physiological cardiovascular changes in pregnancy

Cardiac output

An extra 30–50 mL of oxygen is consumed per minute during pregnancy and an increase in cardiac output is required to meet these extra demands. Stroke volume and heart rate are the two factors that govern cardiac output. The resting cardiac output in females is approximately 4.5 litres per minute. In pregnancy the cardiac output rises by approximately 40% to 6 litres per minute (Figure 1.2). This change occurs early in pregnancy with one half of this increase occurring prior to 8 weeks' gestation. The increase in cardiac output plateaus at 20–30 weeks' gestation. Heart rate increases during pregnancy from 80 beats per minute to 90 beats per minute further contributing to the required increase in cardiac output [5]. In addition there is a decrease in the arteriovenous oxygen gradient, an increase in the preload due to the increase in blood volume, and a reduction in the afterload due to the decline in systemic vascular resistance [6]. The increased cardiac output is distributed throughout the body with the uterus receiving approximately 400 mL/min extra and the kidneys receiving approximately 300 mL/min extra.

During labor significant hemodynamic changes occur due to anxiety, exertion, pain, uterine contractions, uterine involution, and bleeding. These changes may be more significant if the woman is exposed to infection, hemorrhage, or the administration of anesthesia or analgesia. During labor blood from the uterine sinusoids is forced into the systemic circulation with each uterine contraction, thereby increasing preload during labor. Cardiac output increases by 15% above pre-labor levels

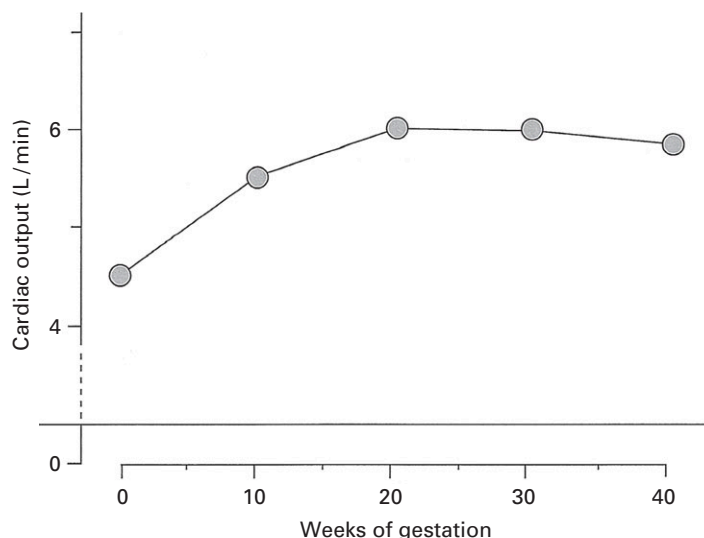


Figure 1.2 Cardiac output in pregnancy. The increase occurs very early and plateaus from approximately 20 weeks of pregnancy.

in early labor and by approximately 25% during the active phase. The additional exertion associated with pushing in the second stage results in a 50% rise in cardiac output. Immediately postpartum, cardiac output increases to 80% above pre-labor values due to significant auto-transfusion associated with uterine involution. It takes approximately three months for the cardiac output and systemic vascular resistance to return to non-pregnant levels.

Blood pressure regulation

In the absence of any pathological process such as preeclampsia, blood pressure remains relatively constant throughout pregnancy. Despite the increases observed in cardiac output, systolic and diastolic blood pressure may drop slightly by up to 5 mmHg and 10 mmHg respectively in the second trimester (Figure 1.3). This occurs due to a decrease in peripheral resistance which exceeds the increase in cardiac output. This decrease in total peripheral resistance accommodates the increased blood flow which is required by various organs and results from a generalized vasodilatation that occurs during pregnancy. The drop

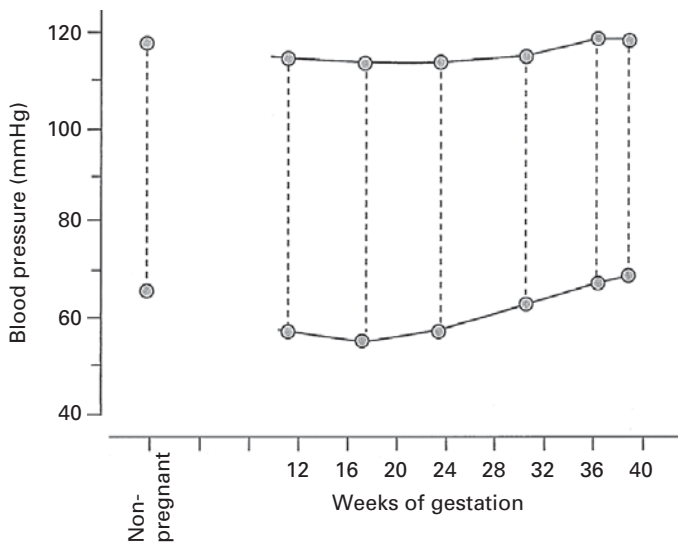


Figure 1.3 Systolic and diastolic blood pressures during pregnancy. The mid-trimester dip found in some women is seen more in the diastolic than in the systolic pressure.

in blood pressure observed in the second trimester recovers, and by term blood pressure levels have returned to normal pre-pregnancy ranges. Central venous pressures, pulmonary capillary wedge pressures, and pulmonary artery systolic and diastolic pressures all remain at a non-pregnant level as increases in cardiac preload and hypervolemia of pregnancy are counterbalanced by falls in both the pulmonary vascular resistance and systemic vascular resistance.

Peripheral resistance is controlled neurogenically by the autonomic nervous system, and directly by substances that act on the blood vessels. These include angiotensin II, serotonin, kinins, catecholamines secreted from the adrenal medulla, metabolites such as adenosine, potassium, hydrogen ions, prostaglandins, and changes in partial pressures of carbon dioxide and oxygen.

In labor and throughout the late second and third trimesters of pregnancy women are advised not to lie directly supine as the gravid uterus compresses the inferior vena cava and decreases the venous return decreasing the cardiac output resulting in hypotension (supine hypotensive syndrome). This hypotension may result in fetal distress secondary to reduced uteroplacental perfusion.

Role of the endothelium in the cardiovascular system

In normal pregnancy the endothelium undergoes many subtle changes in function which contribute to the maintenance of normal cardiovascular function in the mother. The maternal vascular endothelium has many important functions including control of smooth muscle tone through release of vasoconstrictor and vasodilatory substances and regulation of anticoagulation, antiplatelet, and fibrinolytic functions via the release of different soluble factors. The endothelium synthesizes a number of potent vasoactive factors which influence the tone of the underlying vascular smooth muscle. These vasoactive factors include the vasoconstrictors endothelin, angiotensin, and thromboxane. The vasodilators include agents such as nitric oxide (NO) and prostacyclin (PGI₂), the levels of which increase considerably in pregnancy.

In conditions such as preeclampsia there is an abnormal shift towards vasoconstriction. The clinical features of pathological conditions including preeclampsia can be explained as clinical responses to generalized endothelial dysfunction, e.g., hypertension results from disturbed endothelial control of vascular tone, while proteinuria and edema are caused by increased vascular permeability, and coagulopathy is the result of abnormal endothelial expression of procoagulants [7,8]. Underlying endothelial dysfunction is evidenced by decreases in the production of NO and PGI₂, increased production of endothelin, thrombomodulin, and thromboxane, and enhanced vascular reactivity to angiotensin II.

Thromboxane is a member of the eicosanoid family and is produced in platelets by thromboxane-A synthase from the endoperoxides produced by the cyclooxygenase (COX) enzyme from arachidonic acid. Thromboxane acts by binding to any of the thromboxane receptors, which are G protein-coupled receptors coupled to the G protein G_q. Thromboxane is a vasoconstrictor and a potent hypertensive agent, and facilitates platelet aggregation. It is in homeostatic balance in the circulatory system with PGI₂, a related compound. Significant alterations in PGI₂ and thromboxane production occur in women with preeclampsia with studies demonstrating a shift in the renal and vascular PGI₂/thromboxane A₂ ratio towards thromboxane A₂ production, resulting in a tendency to vasoconstriction. Decreases in plasma levels of PGI₂ in women with preeclampsia have been demonstrated as early as 13 weeks' gestation. Prostacyclin is

the predominant vasodilator in pregnancy and is derived from the arachidonic acid pathway after conversion by COX.

The endothelin (ET) family consists of three 21-amino acid peptides (ET-1, ET-2, and ET-3). Endothelins are produced by most cell types in the kidney and have a wide variety of biological actions including regulation of vascular resistance, modulation of fluid and electrolyte transport, and regulation of cell proliferation and extracellular matrix accumulation. Endothelin-1 plays the predominant physiological role in the control of vascular tone and is a highly potent vasoconstrictor agonist. Endothelial damage is a known stimulus for ET-1 synthesis. It is speculated that increases in the production of ET-1 may be involved in the pathogenesis of preeclampsia. These elevated plasma levels of ET-1, which are two- to threefold increased in pregnancy-induced hypertension may have significant long-term effects on systemic hemodynamic and arterial pressure regulation.

Endothelium-derived NO is a key molecule in vascular biology since it is capable of reducing vascular tone, smooth muscle cell proliferation, leukocyte adhesion, and platelet aggregation. Nitric oxide causes relaxation in vascular smooth muscle through activation of soluble guanylate cyclase and subsequent stimulation of cyclic guanosine monophosphate (cGMP). Substantial evidence indicates that NO production is elevated in normal pregnancy and that these increases appear to play an important role in the renal vasodilatation of pregnancy [9]. The increase in NO may be mediated via the ovarian hormone and vasodilator relaxin. The plasma concentration of relaxin rises during pregnancy, a response mediated by human chorionic gonadotropin (hCG). Relaxin is a peptide hormone in the insulin family and it is normally produced in the corpus luteum, but in pregnancy is produced in large amounts by the placenta and decidua. Chronic administration of relaxin to conscious male and castrated female rats mimics the renal hemodynamic changes of pregnancy (20–40% increase in glomerular filtration rate [GFR] and renal plasma flow). These changes are abolished by the administration of a NO synthase inhibitor. The increases in GFR and renal plasma flow in pregnant rats can also be abolished by the administration of antirelaxin antibodies [10].

The actions of hormones derived from the adrenal gland and placenta also appear to play a role in the regulation of blood pressure in normal pregnancy. There is a significant increase in aldosterone levels by the eighth week of pregnancy and this continues to rise to 80 to 100 ng/dL

in the third trimester, fourfold to sixfold above the upper limits observed in non-pregnant adults. Progesterone levels parallel those of aldosterone, reaching a level of 200 ng/dL by term. It is likely that aldosterone is critical in maintaining the sodium balance in the setting of vasodilatation of the peripheral vasculature.

■ **Maternal renal physiological changes in pregnancy**

Normal pregnancy is characterized by increased renal perfusion and several, usually minor changes in extracellular composition, including chronic respiratory alkalosis and hyponatremia [5]. Increased renal perfusion is attributable to the increased cardiac output that occurs during pregnancy.

Renal anatomy

The kidneys increase in size by approximately 1 cm in length secondary to an increase in renal vascular and interstitial volume as opposed to an increase in the number of nephrons. Ureteric dilatation occurs secondary to obstruction of the ureters by the gravid uterus and the smooth muscle relaxation which occurs due to increased circulating levels of progesterone [11]. These raised circulating levels of progesterone also decrease peristalsis and contraction pressure. This dilatation of the upper ureters and pelvic calyces is referred to as the physiological hydroureter of pregnancy. The hydronephrosis which occurs in pregnancy occurs predominantly on the right-hand side (90% vs. 10%). This preference of the right side is most likely explained by anatomical factors. These include dextrorotation of the uterus by the sigmoid colon, kinking of the ureter as it crosses the right iliac artery, and the proximity of the ureter to the right ovarian vein. In addition to the dilatation of the proximal ureters there may also be distal dilatation. The vessels in the suspensory ligament of the ovary enlarge and may compress the ureter at the brim of the bony pelvis, thus causing dilatation above that level. Hypertrophy of Waldeyer's sheath (i.e., the longitudinal muscle bundles in the lower ureter) causes mild stenosis in the juxtavesical region, thereby contributing to dilatation of the ureter above the pelvic brim. These changes result in a physiological dilated collecting system which leads to an accumulation of 200–300 mL of

urine in the collecting system, and this urinary stasis in addition to an increased incidence of vesicoureteric reflux explains why the incidence of urinary tract infections and pyelonephritis increases in pregnancy. The physiological dilatation that occurs also renders ultrasound examination of the renal tract difficult as the only way to differentiate pathological from physiological change is by visualizing the obstruction, which often is not possible with ultrasound alone. During pregnancy the bladder becomes an intra-abdominal organ. Bladder capacity is also decreased by the enlarging uterus which displaces the bladder superiorly and anteriorly.

Ascertainment of symptoms as a sole means of eliciting a urinary tract infection in pregnancy is inadequate as studies have shown that urinary symptoms such as dysuria, polyuria, nocturia, urgency, and stress incontinence occur more frequently during pregnancy even in the absence of pathology [12]. Urinary frequency and nocturia are the commonest urinary symptoms in pregnancy. The increase in urinary frequency most likely occurs due to a combination of increased total urinary output, raised total plasma volume, increases in renal blood flow (RBF) and GFR, and occasionally higher fluid intake [13]. The increased incidence of nocturia in pregnancy appears to result from increased excretion of sodium and solute during the night in pregnancy compared to that in non-pregnant women.

Renal physiology

Renal blood flow rises markedly during pregnancy. It increases by 75–80% above non-pregnant values to at least 1.5 L/min in pregnancy and this change is evident within the first trimester. Glomerular filtration rate rises from 140 to 170 mL/min and similar to the RBF the increase in GFR can be demonstrated within one month of conception and reaches a peak approximately 40–50% above baseline levels by the end of the first trimester [14]. The increase in GFR is due solely to an increase in glomerular plasma flow and not increased intraglomerular capillary pressure. With the increase in GFR, there is an increase in endogenous clearance of creatinine.

Antidiuretic hormone (ADH) activates the vasopressin-2 receptor on the renal collecting ducts to stimulate water absorption. The release of vasopressinases from the placenta results in an approximate fourfold increase rate of ADH catabolism. However, plasma levels of ADH remain normal because of a fourfold rise in the production of ADH by the