PART I

Physiologic Changes During Normal Pregnancy and the Puerperium

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CHAPTER 1

Hemodynamics and Cardiac Function

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Introduction

Pregnancy is associated with marked physiologic changes that require adaptation of the cardiovascular (CV) system. These changes result in a substantial increase in circulatory burden that can unmask previously unrecognized cardiac disorders, lead to a rapid deterioration of heart disease and result in a significant maternal morbidity or even mortality along with important effects on fetal outcome. A comprehensive understanding of cardiocirculatory adaptation during pregnancy and the early postpartum (PP) period is critically important for the management of pregnant patients with CV disease.

Cardiovascular effects of pregnancy-related hormonal changes

To better understand the complex hemodynamic changes associated with pregnancy, the cardiac effect of pregnancy-related hormonal changes needs to be described.

Estrogen and progesterone

Early pregnancy is characterized by an increase in the levels of estrogen and progesterone. The CV effect of estrogen is complex; laboratory models have demonstrated that estrogen induces nephron sodium resorption [1] and increases the levels of angiotensin (ANG) II [2]. At the same time, however, estrogen was also shown to activate type 2 ANG II receptors [3] and can increase the levels of nitric oxide (NO) through the stimulation of NO synthase [4] with consequent vasodilation. Progesterone was reported to block the sodium-retaining effect of aldosterone [5] and was found to induce a direct natriuretic effect on the kidneys [6]. In a laboratory rat model [7], progesterone ameliorated the hypertensive effect of norepinephrine in the intact animals and blunted the vasoconstrictive effect of vasopressin and calcium channel current in isolated vascular smooth muscle cells, suggesting that its vasodilatory effect might be through a decrease in intracellular calcium content [7]. Altogether, estrogen probably has a neutral effect on blood pressure (BP), while progesterone induces significant vasodilation.

Relaxin

A peptide hormone mainly secreted by the female reproductive system [8]. Although originally named after its ability to induce pelvis, uterine, and cervix relaxation prior to delivery [9], relaxin was found to induce significant CV changes. Compared with levels of 10 pg/ml found in men and postmenopausal women, relaxin levels peak to 900 pg/ml in early pregnancy [10]. Relaxin exerts its CV effects mostly through the relaxin-family peptide receptor type 1, an abundant receptor found not only in the reproductive system but also in the heart, lungs, kidneys, and the brain [11]. Studies in nonpregnant animals have shown that intravenous administration of relaxin reduced BP and systemic vascular resistance (SVR) and also increased cardiac output (CO) [12,13]. Similarly, pregnancy-related CO increase was blunted in animals exposed to relaxin-neutralizing antibodies [14]. A laboratory model of resected human arteries showed a significant endothelium-dependent vasodilating effect of relaxin [15]. Other studies demonstrated that relaxin-induced vasodilation was NO-dependent [16], and also, that relaxin stimulated the expression of endothelial (but not vascular smooth muscle) endothelin type B receptors, with consequent increase in endothelin clearance and endothelial release of NO, leading to increased vasodilation [17]. Additionally, the administration of relaxin has been shown to induce an increase in renal blood flow and glomerular filtration rate in nonpregnant rats [18], whereas relaxin-neutralizing antibodies prevented renal vasodilation and pregnancy-related glomerular filtration rate increase in pregnant rats [19].

Natriuretic peptides

These peptides are known to induce vasodilation and natriuresis, blunt the effect of catecholamines, and prevent cardiac remodeling [20]. Levels of B-type natriuretic peptide (BNP)

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and NT-proBNP have been shown to be significantly elevated during normal pregnancy, although their levels remained within normal range throughout gestation [21–23]. In a longitudinal study, BNP levels were measured in each trimester and four to six weeks postpartum in 29 women and in 25 healthy matched controls [24]. Overall, median BNP levels were 10 pg/ml in the control group and 19 pg/ml in the pregnancy group ($p = 0.003$). However, no statistically significant difference was found between median BNP levels in the first (20 pg/ml), second (18 pg/ml), and third (26 pg/ml) trimesters or four to six weeks postpartum (18 pg/ml). Notably, BNP levels as high as 143 pg/ml were measured in some women during the third trimester of normal pregnancy [24]. Similar mild but significant increase in NT-proBNP levels were found by Franz *et al.* during the first two trimesters in 94 normal pregnant women [22]. Lev-Sagie *et al.* [23] measured N-terminal proBNP in 88 healthy pregnant women and showed doubling of the levels within 28 hours postpartum compared with predelivery levels (165 ± 102 pg/ml vs. 81 ± 32 pg/ml, $p < 0.001$). This increased level of natriuretic peptides in the early postpartum period is probably related to the increased venous return to the heart and results in increased diuresis after the delivery.

Renin–angiotensin–aldosterone system

Compared with nonpregnancy state, higher levels of angiotensinogen (AT), ANG II, renin, and plasma renin substrate have been demonstrated in normal pregnancy [25]. Both AT and ANG II levels were reported to rise progressively throughout pregnancy. Plasma prorenin levels peak during the first trimester whereas active renin levels increase during the second trimester, and angiotensin converting enzyme levels remain stable throughout pregnancy [26,27]. Notably, aldosterone levels are increased beyond those expected by renin and ANG II levels, resulting in an increased aldosterone: renin ratio in pregnancy [28,29]. A possible cause for this finding could be the effect of placenta-originated elevated levels of vascular endothelial growth factor (VEGF) on aldosterone production. In a laboratory model, Gennari-Moser *et al.* demonstrated that VEGF directly increased the production of aldosterone from adrenocortical cells and, in addition, synergistically increased the effect of ANG II-mediated aldosterone synthesis [30]. The vasoactive effect of angiotensin II is not straightforward; it can bind to both ANG II type 1 receptors (with consequent vasoconstriction) and to ANG II type 2 receptors (with consequent vasodilation). In pregnancy, the density and the response of ANG II receptors change, with a propensity toward higher activity of the vasodilating angiotensin II type 2 receptors [31,32]. High levels of ANG II play a role in maintaining blood volume, BP, and uroplacental blood flow by the interaction with the ANG type I and II receptors [27].

The sympathetic system

Sympathetic hyperreactivity was originally thought to occur only in pregnancy-related hypertensive disorders [33]. However, in 2001, Greenwood *et al.* compared normotensive, nonpregnant women with age and race matched women at 35-week gestation with either normal pregnancies or pregnancy-induced hypertension (PIH) [34]. The study showed a statistically significant elevation of sympathetic activity and impaired baroreflex sensitivity in normal pregnancy compared with nonpregnant state, (albeit to a lesser degree compared with PIH), which returned to nonpregnancy values after the delivery. Similar results were reported by Jarvis *et al.* [35] who found an increased sympathetic tone as early as six-week gestation compared with prepregnancy state, despite reduced diastolic BP and vascular resistance. This change in sympathetic activity was accompanied by elevated levels of noradrenaline and renin [35]. The mechanism for increased sympathetic tone in early pregnancy is not completely clear and is probably multifactorial. Studies have suggested that elevated levels of estrogen [36], ANG II [37], and aldosterone [38] might stimulate the sympathetic system. Another explanation for the elevated sympathetic tone during pregnancy is probably related to a compensatory mechanism to the pregnancy-related peripheral vasodilation [35].

Hemodynamic changes during pregnancy

Blood volume

An increase in blood volume of 34–70% (50% average) compared with nonpregnancy levels is seen by the third trimester of normal pregnancy, and plasma volume ranging from 3200 to 4280 ml/m^2 (depending on parity) is found in a normal singleton pregnancy [39,40]. The rise in volume starts as early as in the fourth gestational week, it is increased 10–15% by the 6–12 weeks with continuous rises until parturition (Figure 1.1). The mechanism leading to hypervolemia in pregnancy seems to be multifactorial (Table 1.1). Both estradiol and progesterone have been found to have important effects on body water primarily by increasing renal sodium and water retention [42]. Increase of aldosterone production mediated by progesterone, ANG II, and plasma originated VEGF results in increased sodium reabsorption [27]. The threshold for vasopressin secretion decreases in pregnancy due to a reset of osmoregulation. In addition, the threshold of thirst was also found to be reset at a lower plasma osmolality level facilitating water retention [43]. The peripheral arterial dilatation with relative under filling of the arterial circulation has been suggested to lead to stimulation of the renin–ANG–aldosterone axis and contribute to the sodium and water retention [44]. Ohara *et al.* have also shown an up-regulation of the collecting duct aquaporin 2 channels in pregnant rats, which play a pivotal role in renal water regulation and may contribute to water retention in pregnancy [45].

Red blood cell mass increases by 33% during normal pregnancy and constitutes a significant proportion of blood volume expansion [46,47]. The mechanism for red blood cell mass increase is complex; erythropoietin concentration

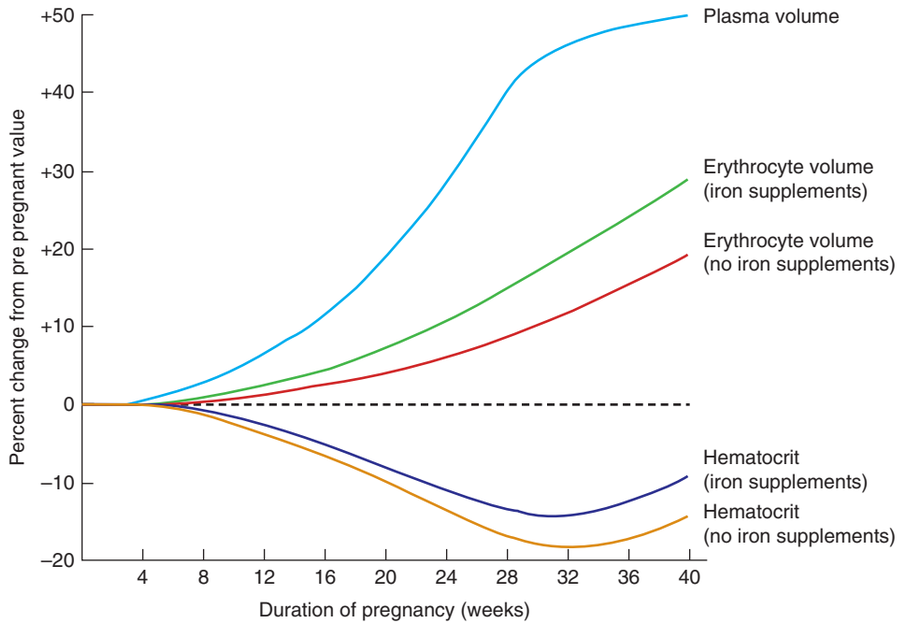

Figure 1.1 Changes in plasma volume, erythrocyte volume, and hematocrit during pregnancy. Increase in plasma volume is more rapid than the increase in erythrocyte volume, causing the "physiological anemia of pregnancy." Source: Pitkin 1976 [41]. Reproduced with permission of Wolters Kluwer Health, Inc.

in the plasma and urine of pregnant women increases only slightly during early pregnancy, and it peaks around mid-pregnancy and decreases thereafter [48]. This pattern contrasts the continued increase in red blood cell mass throughout pregnancy. Jepson reported that higher degree of erythropoietin activity was measured in blood vessels draining the gravid uterus compared with peripheral blood, indicating that a certain factor (now recognized as human placental lactogen) increases erythropoietin activity during pregnancy [49]. A second potential explanation may be related to the elevated levels of progesterone during pregnancy and the peripartum period, which neutralizes the negative effect of estrogen on production and activity of erythropoietin [49]. It should be also noted that prolactin, a hormone biologically similar to human placenta lactogen, also enhances, synergistically, the effect of endogenous erythropoietin during lactation. The larger increase in plasma volume during pregnancy compared to that of red blood cell mass results in the "physiologic pregnancy-related anemia" found in most pregnant women. Meta-analysis of collected data showed a decrease in hematocrit from prepregnancy value of $39 \pm 2.5\%$ to $37 \pm 3\%$ at 17 weeks, $36 \pm 6\%$ at 27 weeks, and $34 \pm 3\%$ at 39 weeks' gestation [40]. Importantly and paradoxically, the physiologic anemia of pregnancy occurs concomitantly with an increasing need of the developing fetus for oxygen. As a compensatory mechanism, increased levels of erythrocyte 2,3-diphosphoglycerate are found in pregnant women and contribute to an increased dissociation of oxygen from the mother's hemoglobin and elevated levels of oxygen delivered to the fetus [50].

Table 1.1 Potential mechanisms of pregnancy-induced increased blood volume

Increased sodium and water retention due to:
- Increased levels of estrogen and progesterone
- Increased aldosterone production stimulated by progesterone, angiotensin II, and plasma originated VEGF
- Decreased threshold for vasopressin secretion due to reset of osmoregulation
- Reset of threshold for thirst at lower plasma osmolality level
- Stimulation of renin–angiotensin–aldosterone axis due to peripheral vasodilation
- Up-regulation of collecting duct aquaporin 2 water channels

Increased red blood cell mass due to:
- A mild increase in plasma erythropoietin levels
- Augmentation of erythropoietin activity by increased levels of human placental lactogen and prolactin
- Counteraction of the negative effect of estrogen on erythropoietin production and activity by increased levels of progesterone
- Increased iron absorption and utilization

Cardiac output

Bader *et al.* in 1955 used right heart catheterization with Fick method to show an increase in CO reaching its peak by the end of the second trimester and decreasing thereafter toward prepregnancy values by the end of the third trimester (Table 1.2, Figure 1.2) [52]. This study, however, was not longitudinal and was done in five different groups of women at different phases of pregnancy (none prior to

Table 1.2 Circulatory changes during normal pregnancy

	Changes at various times (wk)					
Parameters	**5**	**12**	**20**	**24**	**32**	**38**
Heart rate	↑	↑↑↑	↑↑↑	↑↑↑↑	↑↑↑↑	↑↑↑↑
Systolic blood pressure	↔	↓	↓	↔	↑	↑↑
Diastolic blood pressure	↔	↓	↓↓	↓	↔	↓↓
Stroke volume	↑	↑↑↑↑↑	↑↑↑↑↑↑	↑↑↑↑↑↑	↑↑↑↑↑	↑↑↑↑↑
Cardiac output	↑↑	↑↑↑↑↑↑	↑↑↑↑↑↑↑	↑↑↑↑↑↑↑	↑↑↑↑↑↑↑	↑↑↑↑↑↑↑
Systemic vascular resistance	↓↓	↓↓↓↓↓	↓↓↓↓↓↓	↓↓↓↓↓↓	↓↓↓↓↓↓	↓↓↓↓↓
Left ventricular ejection fraction	↑	↑↑	↑↑	↑↑	↑	↑

↑ – ≤5%; ↑↑ – 6–10%; ↑↑↑ – 11–15%; ↑↑↑↑ – 16–20%; ↑↑↑↑↑ – 21–30%; ↑↑↑↑↑↑ – >30%; ↑↑↑↑↑↑↑ – >40%.
Source: Based on data by Robson *et al.* 1989 [51].

14th week gestation due to the concern of fetus exposure to radiation). In 1966, Walters *et al.* [53] confirmed these findings with serial evaluations of CO using a dye dilution technique in 30 women throughout pregnancy. The introduction of echocardiography, which safely allowed the serial evaluations of pregnant women throughout pregnancy [51,54–58], showed that the start of CO rise in pregnancy was early and occurred by week 5. From the systematic review on CO in pregnancy conducted by van Oppen *et al.* [59], five studies of genuine longitudinal design could be identified; all reported a rise in CO which occurred early in the first trimester, with further increase in the second trimester. Reported change in CO between the second and third trimester were diverse; one study showed further increase [57], two showed no change [51,60], and the last two demonstrated a decrease [61,62]. Conclusions regarding the total increase in CO during pregnancy can be best derived from the echocardiographic study by Robson *et al.* [51], who uniquely measured baseline CO before conception and showed 11% increase by fifth gestational weeks, 34–39% at 12 weeks and 50% rise (from 4.88 to 7.34 l/min) at 34 weeks (Figure 1.2). Atkins *et al.* [62] used impedance cardiography for the serial measurements of CO in a group of eight women from preconception along pregnancy and up to 4–16 months postpartum. The authors did not provide specific CO values; however, a graph showed an initial increase, reaching its peak by 20 weeks and declining thereafter to levels lower than prepregnancy at term. It is possible that these unique results were derived from water and salt accumulation in late stages of pregnancy, which might have affected CO readings with the use of impedance

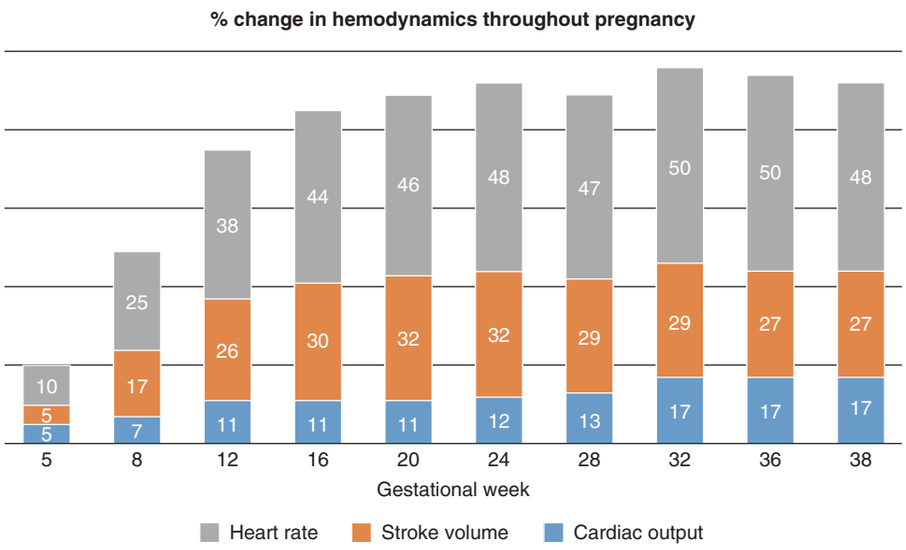

Figure 1.2 Percent changes of heart rate, stroke volume, and cardiac output measured in the lateral position throughout pregnancy compared to prepregnancy values. Source: Based on data by Robson *et al.* 1989 [51].

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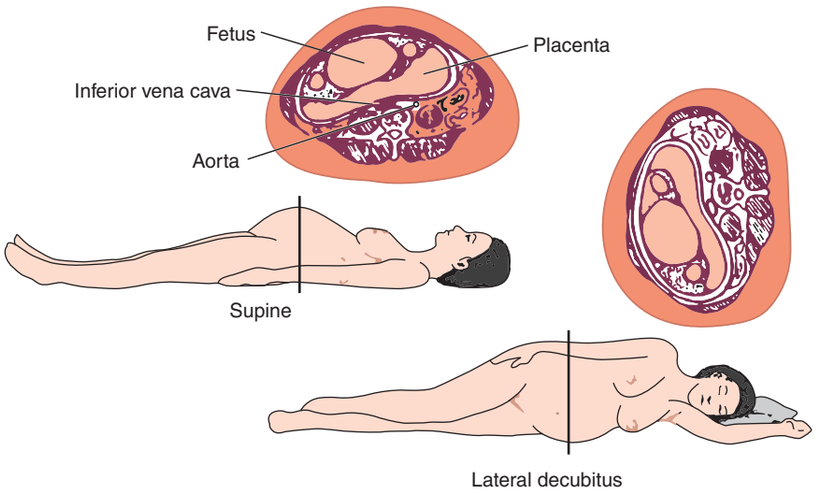

Figure 1.3 After about 20 weeks of gestation, vasocaval compression of the inferior vena cava can lead to reduced venous return and thus to decreased cardiac output and blood pressure.

cardiography in this study. A contemporary serial echocardiographic examination of 51 women in each pregnancy trimester and three to six months postpartum showed a 19% higher CO during the first trimester compared to 10 nonpregnant age-matched women, which further increase to 29% and 37% during the second and third trimesters, respectively [63].

The overall increase in CO observed in normal pregnancy is achieved initially through an increase in both heart rate and stroke volume (SV) and a continued increase in heart rate starting at midterm until the end of pregnancy [56,60,63] (Figure 1.2).

Recent utilization of magnetic resonance imaging (MRI) for the serial measurements (12–16 weeks, 26–30 weeks, 32–36 weeks, and 12 weeks postpartum) of CO during pregnancy in a cohort of 23 women [64] confirmed a significant early increase in CO, which reached its peak at 26–30 weeks and remained stable at 32–36 weeks [64]. A study comparing MRI with echocardiography in women in the third trimester and 12 weeks PP showed a similar >50% increase in CO between nonpregnant state and third trimester pregnancy with the use of both modalities [65]. MRI measurements, however, tended to be 10–15% higher for both pregnant and nonpregnant states.

Twin pregnancy

Robson *et al.* reported a significantly larger increase in CO during twin compared to singleton pregnancy, mainly because of a larger increase in heart rate [66]. These findings were confirmed by Kametas *et al.* [67], who performed an echocardiographic study in 119 pregnant women with twin pregnancies at 10–40 weeks gestation and compared the measurements with those obtained from 128 women with singleton pregnancies. Maternal CO was greater in twin pregnancies by 20%. In addition, women with twin pregnancies had greater left ventricular (LV) dimensions, systolic function, and mass.

Effect of maternal posture

After about 20-week gestation, maternal posture has a significant effect on CO [68], and changing from a supine to lateral position results in a marked increase in CO due to reduced caval compression (Figure 1.3). A recent MRI study by Rossi *et al.* [69] demonstrated 35% and 24% position-related increase in SV and CO, respectively, in a group of healthy women in their late pregnancy. In spite of this change in CO in the supine position, BP is maintained in most women due to a compensatory rise in SVR.

Supine hypotensive syndrome of pregnancy

This can be found in up to 15% of term pregnancies and is defined as a decrease in systolic BP of at least 15–30 mmHg in the supine position. Symptoms develop within 3–10 minutes after lying down and usually include weakness, dizziness, nausea, diaphoresis, and even syncope [70] as a result of a 30–40% decrease in CO and BP due to compression of the inferior vena cava (IVC) by the gravid uterus with resultant decrease in venous return to the heart. Maternal and fetal death has been reported in extreme cases [71]. A limited form of the syndrome may be more prevalent and includes asymptomatic CO and BP decrease in supine position, which can deteriorate to the full clinical picture in case of sympathetic blockade (e.g. spinal anesthesia) [72]. Nevertheless, considering the significant compressive effect of the gravid uterus on the IVC, it is surprising that only a relatively small proportion of women demonstrate this syndrome. A possible protective mechanism is the development of collateral venous drainage through the vertebral vessels as was described by Scott and Kerr [73]. Another proposed protective mechanism of an increased baroreflex response and a compensatory increase

in heart rate was refuted by Lanni *et al.*, who showed that compared with nonaffected third trimester women, those with the syndrome had a higher degree of tachycardia [74].

Systemic vascular resistance

A significant decrease in SVR in pregnancy compared with nonpregnant state has been demonstrated in numerous studies using different methodologies. The early invasive study by Bader *et al.* [52] showed the lowest SVR in the second trimester. Another invasive hemodynamic study reported a significant decrease in SVR in late pregnancy compared to 12-week postpartum [75]. In this study, however, no measurements were made in the first or second trimesters of pregnancy. With the use of echocardiography, Robson *et al.* showed a gradual fall in SVR starting as early as 5-week gestation (9%) with a maximum decrease of 34% at 20 weeks followed by a plateau between the 20th and 32nd week, and a slight increase from week 32 to term [51]. Despite this late increase, SVR was still lower by 27% compared to the preconception levels. Savu *et al.* [63] showed close to 20% reduction in SVR during pregnancy compared to both age-matched control and postpartum values, with further decrease of about 30% during the second and third trimesters.

There are multiple mechanisms, which contribute to the fall in SVR during pregnancy (Table 1.3). These include the vasodilatory effect of pregnancy hormones as well as relaxin and natriuretic peptides and an increased resistance to the pressor effect of angiotensin and noradrenalin [76,77]. A number of investigators have also reported enhanced endothelium-dependent flow-mediated vasodilation during gestation [78,79] and an increase in NO production throughout normal pregnancy, which returned to nonpregnant levels by 9–12 weeks PP [80,81]. In addition, increased levels of prostacyclin may lead to direct vasodilation [82]. Poppas *et al.* [83] showed an increase in arterial compliance and distensibility, beginning in the first trimester of pregnancy. Similarly, Macedo *et al.* [84] showed a reduction in aortic wave reflection (a measure of aortic stiffness), which reached its nadir in the second trimester. This increased compliance might be due to elevated levels of estrogen and increased prevalence of estrogen receptors in the endothelium and vascular smooth muscle [85]. This assumption is supported by similar vascular changes found both in animal models and in transsexual men exposed to estrogen [86,87]. Additionally, vessel wall histologic changes, including alteration in collagen/elastin ratio, have been reported in pregnancy and might affect arterial compliance and vascular resistance [88,89]. Finally, pregnancy is a proangiogenic state, the growth of the low-resistance, high-flow uteroplacental circulation increases blood supply to the growing uterus and affect SVR. Jaffe and Warsof [90] and Jurkovic *et al.* [91] have demonstrated that shunting of blood from the systemic circulation to the uteroplacental circulation increased during the first and second trimesters of pregnancy and that diastolic blood flow to the uteroplacental circulation was shown as early as the first few weeks after conception. Coppens *et al.* [92] further showed that resistance dropped to a higher degree at earlier stages of pregnancy in the blood vessels surrounding the trophoblast, indicating the probable effect of trophoblast implantation on local vascular resistance. The marked increase in vascularity to the mammary vascular bed may also play a role in the overall reduction in SVR.

Table 1.3 Potential mechanisms for pregnancy-induced systemic vascular resistance reduction

- Vasodilatory effect of increasing levels of estrogen, relaxin, natriuretic peptides, and prostacyclin
- Increased prevalence of estrogen receptors in blood vessels
- Increased vessel wall relaxation and distensibility through flow mediated, endothelium dependent, vasodilation
- Increased nitric oxide production throughout pregnancy
- Increased resistance to the vasoconstrictive effect of angiotensin and noradrenaline
- Increased arterial compliance
- The development of a low resistance, high flow uteroplacental circulation
- Increased mammary vascularity

Blood pressure

Despite different methods and devices used for BP measurement in different studies which could have produced dissimilarities in the data collected, pregnancy-induced BP drop was reported in most studies and is probably the consequence of a higher degree of SVR reduction compared with the degree of CO increase in pregnancy [93–96]. The decrease in BP is most significant in the initial few weeks after conception [93,97], and accordingly, might be missed if the patients are first evaluated at a later stage of pregnancy. This decrease in BP is mostly driven by a drop in diastolic BP and, to a lesser degree, by a reduction in systolic BP, leading to an increase in pulse pressure [98]. The continued BP decrease between the first and second trimesters is less significant compared to the one seen between prepregnancy and first trimester. However, most studies reported on a nadir in BP drop around midpregnancy [93–96]. A mild increase in BP is usually found during the third trimester and continues toward delivery and the PP period. Nevertheless, 2–3 mmHg lower BP levels compared to prepregnancy values can be found up to 16 weeks PP [93]. Although within normal range, higher body weight and older age were shown to be associated with higher BPs during pregnancy [99,100] and might predispose these women to PIH and preeclampsia.

Heart rate

Heart rate rises gradually during pregnancy (Figure 1.2) with a mean maximum increase of about 10–20 beats per minute [51,57,63]. Occasionally, women present with inappropriate sinus tachycardia with rates >100 bpm and even >120 bpm,

which are usually well tolerated [101] and do not have an effect on LV function (personal observation).

Pulmonary artery pressure and pulmonary vascular resistance (PVR)

In the early study by Bader *et al.* [52], who performed cardiac catheterization in 46 normal pregnant women at different stages of pregnancy, normal pulmonary pressures were recorded both at rest and during exercise throughout pregnancy. Although pulmonary artery wedge pressure was not measured, the significant increase in CO indicated a substantial reduction in total pulmonary vascular resistance (PVR) [52]. Similar findings were reported by Clark *et al.* who described no significant changes in invasively measured pulmonary pressures at 36–38 weeks compared with 12-week postpartum. No hemodynamic measurements were performed, however, during the first or second trimesters [75]. A later study by Robson *et al.* [102] reported serial pulmonary hemodynamic assessments using Doppler and cross-sectional echocardiography in 13 women prior to conception, at monthly intervals throughout pregnancy, and six months after delivery. Baseline mean pulmonary artery pressure was 14 mmHg with no significant change during pregnancy. Pulmonary resistance decreased by 24% at eight weeks without a further significant change later on. Values returned to prepregnancy levels by six months PP [102]. A recent echocardiographic study assessed serial hemodynamic changes during the course of pregnancy in 60 pregnant women compared to 15 nonpregnant control women matched by age and body size [103]. This study confirmed previous reports and demonstrated normal pulmonary artery pressures during the first trimester without a significant change later in pregnancy. In the second trimester, pulmonary blood flow was increased by 29% and PVR decreased by 15% compared to the first trimester. A further 13% increase in pulmonary blood flow and 17% decrease in PVR were seen during the third trimester [103].

Cardiocirculatory changes during labor and delivery

Labor, delivery, and the early PP period are associated with marked and sudden changes in hemodynamics [104]. During labor, the combination of increased blood volume and venous return to the heart from the contracting uterus and increased heart rate and myocardial contractility mediated by catecholamine surge results in significant hemodynamic changes. Seminal early report by Ueland and Hansen [105] who studied 23 supine laboring women during the first stage of labor and before sedation showed an average increase of 33% in SV with each uterine contraction accompanied by a reflex 15% decrease in heart rate resulting in a 24% rise in CO and 26% rise in pulse pressure. It should be noted that during each contraction, there is a complete occlusion of the distal aorta and/or common iliac arteries resulting in an increase in BP measured in the upper extremities but a decrease in BP measured in the femoral arteries [106]. Compared with supine position, the hemodynamic changes during labor were significantly different in the lateral position. Because venous return was maintained at all times and there was less obstruction of the distal aorta during contractions, higher CO and SV were measured. Changes during contractions in the lateral position were much smaller with only 8% increase in SV and CO, no change in heart rate and only a small change in BP. A later assessment of CO during labor in the semilateral position using Doppler and cross-sectional echocardiography of the pulmonic valve showed a progressive increase in the rise in CO during uterine contraction [107]. At ≥8 cm cervical dilatation, CO increased >30% as a result of a rise of both SV and heart rate and was accompanied by a 10% increase in mean BP. It should be noted that all women were given pethidine and nitrous oxide for analgesia and did not have epidural labor analgesia [107]. This fact is of great importance because the form of anesthesia plays a substantial role in modifying the CV response to labor and delivery. Under local anesthesia, CO showed progressive increase throughout labor. The changes were less striking during caudal anesthesia [108], partially because of better control of pain. Similar changes were recorded in both groups of patients during the Valsalva maneuver, which was associated with a marked increase in systemic BP and central venous pressure [108].

The effect of cesarean section (CS) on maternal hemodynamics

Performing cesarean section (CS) prior to onset of labor can prevent the hemodynamic changes observed during contractions but can result in cardiocirculatory responses related to the use of anesthetics and to surgery. The hemodynamic effect of CS is greatly influenced by the mode of anesthesia used and the type of drugs utilized during the operation. A series of studies by Ueland *et al.* [109–111] evaluated the hemodynamic effects of CS delivery at term under various forms of anesthesia. In women receiving local anesthesia during labor in the supine position, there was a progressive increase in CO measured by the dye dilution technique which reached 25% above prelabor values at the late first stage, 49% at the second stage, and 80% immediately after delivery [108]. In women receiving caudal analgesia, the corresponding figures were 21%, 24%, and 59% respectively. Although caudal anesthesia attenuated CO increase during labor and after the delivery, both techniques were associated with a similar 15–20% increase in CO during uterine contractions regardless of the stage of labor [108]. The effect of general anesthesia using thiopental, nitrous oxide, and succinylcholine was investigated in 17 normal pregnant women undergoing repeat CS at term [111]. Baseline CO before anesthesia increase 29% and heart rate decreased 16% in the lateral compared to supine position. During anesthesia, CO increased only slightly, and intubation was associated

with additional 16% increase in CO, 18% in heart rate, and 14% in BP. Peak CO increase (41% over control) was seen 10 minutes after the delivery. Notably, the reflex tachycardia and hypertension associated with endotracheal intubation has been shown to be associated with profound decrease in LV ejection fraction and an increase in LV filling pressure in nonpregnant patients with mild LV dysfunction [112]. Spinal anesthesia was reported by Ueland and coworker to be associated with a significant decrease in BP prior to the onset of surgery [104]. These findings were later confirmed by Langesaeter *et al.* [113], who performed a double-blinded study in 80 healthy women scheduled to undergo an elective CS who were randomized to spinal aesthesia with low vs. high dose bupivacaine with or without a concomitant infusion of low-dose phenylephrine. The study showed a marked decrease in mean BP in both the low- and the high-dose groups mediated by a fall in SVR, despite a substantial increase in CO. This decrease in BP was significantly attenuated by phenylephrine in the low dose group, suggesting that this approach combined with moderate rehydration gives the best hemodynamic stability during spinal anesthesia for CS. Similar to spinal anesthesia, the use of epidural anesthesia with epinephrine was associated with preoperative hypotension in all patients and often required treatment including uterine displacement, and/or intravenous fluid and/or compression bandaging of the lower extremities in addition to intravenous vasopressors [104]. In contrast, epidural anesthesia without epinephrine was reported to be associated with better hemodynamic stability during surgery and at delivery [109]. There were, however, minor changes in CO and heart rate following the administration of anesthesia with a transient decline in BP that could be corrected by uterine displacement without the need for vasopressor drugs. Milsom *et al.* [114] compared hemodynamic changes during CS in 20 women treated with either epidural or general anesthesia. In women receiving epidural anesthesia, CO increased significantly before delivery, largely as a result of a significant increase in heart rate, with further increase after the delivery. There was also a significant decrease in systolic and diastolic BP as a result of a fall in SVR. General anesthesia was associated with a significant decrease in SV during the delivery, while CO did not change (because of a marked increase in heart rate), but increased after delivery probably due to increased venous return. In contrast to epidural anesthesia, general anesthesia was associated with a significant increase in both systolic and diastolic BP due to increased SVR [114]. Milsom *et al.* also investigated the effect of change in body position before and after the delivery on maternal circulation in patients undergoing epidural anesthesia. Assumption of the supine position before delivery was associated with a significant reduction in CO and SV and a significant increase in heart rate, SVR, and BP. In contrast, the supine position postpartum was associated with only minor and insignificant hemodynamic changes [114].

In summary, hemodynamic changes during CS are influenced considerably by the patient's position and the form of anesthesia or analgesia used. Marked variations have been demonstrated among various anesthetic techniques and anesthetic agents that need to be taken into account in the delivery plan of the cardiac patient.

Hemodynamic changes during the puerperium

Major hemodynamic changes occur immediately after the delivery (Figure 1.4) [116]. CO and SV have been reported to increase >50% [105] probably as a result of an "auto transfusion" from the contracting uterus and an increase in venous return to the heart due to relief of IVC compression by the gravid uterus [117]. At 1 hour following delivery, heart rate and CO returned to prelabor values, whereas BP and SV remained elevated and returned to prelabor values at 24 hours PP [107,118]. Evaluation of hemodynamic at 38 weeks gestation, 48 hours and two weeks PP in 10 healthy women in the semilateral position showed that CO remained elevated for at least 48 hours after the delivery due to increased SV and despite a substantial fall in heart rate. At two weeks PP, CO decreased significantly owing to decline in SV and further decrease in heart rate [117]. The same group reported on hemodynamic evaluation of 15 healthy women at 38-week gestation and at 2, 6, 12, and 24 weeks postpartum. Both CO and heart rate fell progressively and returned to predelivery values at two weeks after the delivery, whereas SV was reduced only partially at two weeks and showed a further decline by 6 months [115] (Figure 1.4). A unique study by Capeless and Clapp [119] compared hemodynamic parameters in 13 women before conception and at 6 and 12 weeks postpartum. Hemodynamic parameters as well as LV dimensions were studied with M mode echocardiography in the left lateral position. While heart rate returned to preconception values, SV, CO, and LV end diastolic volume remained significantly elevated both at 6 and 12 weeks postpartum, and SVR remained decreased.

Robson *et al.* evaluated the effect of postpartum hemorrhage in 10 women with estimated blood loss of >500 ml (550–1900 ml) in comparison with a control group of 30 women who had uncomplicated labor (estimated blood loss 50–400 ml), during which they received an average of 280 ml of intravenous fluid. All women received syntometrine at the time of delivery. Compared to the control group, SV decreased and heart rate increased in the patients with PP hemorrhage. Nevertheless, CO and BP were the same due to higher heart rate and SVR [120].

In summary, significant hemodynamic changes are seen in the immediate PP period. These changes may be affected by the amount of blood loss. In women with uncomplicated delivery, there is a marked increase in CO despite a rapid decline in heart rate, which remains higher than the prelabor value for at least 48 hours. Postdelivery hemodynamics return fairly rapidly toward prelabor values, but complete return to preconception values occurs only after several weeks to months.

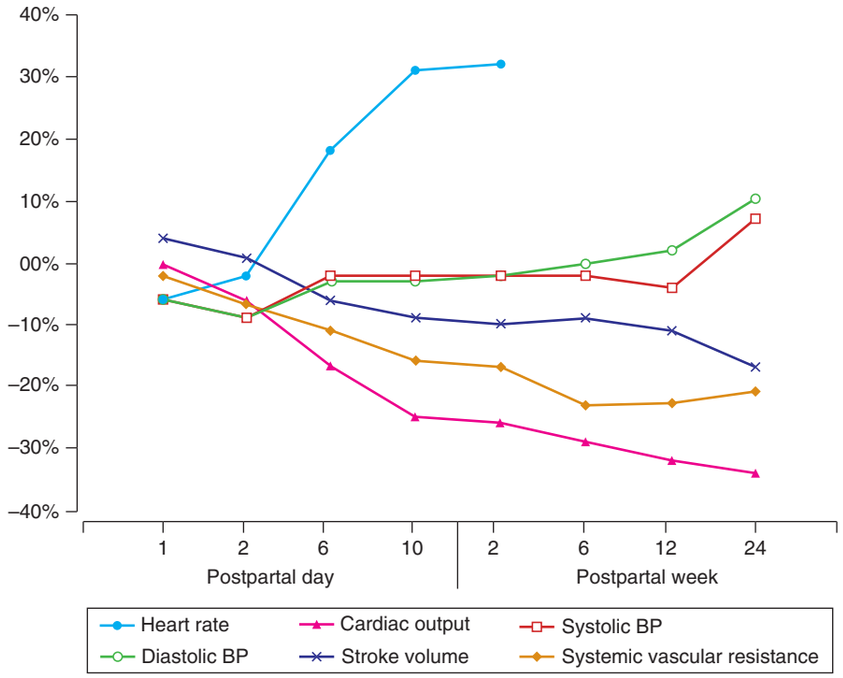

Figure 1.4 Percent postpartum changes in hemodynamic parameters compared to 38 weeks gestation. Source: Based on data by Robson *et al.* 1987 [115].

Structural and functional cardiac changes

Dimensions

Pregnancy is a state of volume overload, and the woman's heart usually responds to this new state with a small increase in dimensions and mass. Echocardiography has been the most widely used tool for the evaluation of pregnancy-associated structural changes. While few studies showed no significant increase in cardiac chambers dimensions during pregnancy [58,121], most studies have demonstrated a small yet significant increase in the size of the LV (i.e. LV end systolic diameter, LV end diastolic diameter, LV volume) and the left atrium [63,65,122–124] which remain, however, within normal limits. A recent study by Savu *et al.* have shown a maximum increase of most measures in the second and third trimesters, including an 8% increase of LV end diastolic dimension, 15% of LV end systolic dimension, 33% of LV end diastolic volume, 31% of LV end systolic volume, and 20% increase in left atrial area [63]. The same investigators also reported a reduction in sphericity index (indicating that the LV becomes more globular) as pregnancy progressed [63]. Left ventricular mass was shown to increase by more than 30% in the third trimester compared with baseline measures. The study of Cardiac Hemodynamic Imaging and Remodeling in Pregnancy (CHIRP) examined the change in cardiac chamber size during the third trimester compared to four months PP with both echocardiography and MRI and showed a 50% increase in LV mass [65]. A good correlation was found in changes of LV end diastolic volume and LV mass between the two imaging modalities, but the values were somewhat underestimated by echocardiography. Though the data on the right heart are more scares, studies have also shown an increase in right ventricular (RV) and right atrial dimensions throughout pregnancy [125]. In the CHIRP study, compared with four months PP, MRI measurements at the third trimester showed an increase in RV end diastolic dimension from 33 ± 4 to 39 ± 3 mm, RV volume from 93 ± 4 to 115 ± 4 ml, and RV mass from 51 ± 5 to 71 ± 6 gr (all $p < 0.05$) [65]. LV outflow tract diameter was shown to either increase [58] or remain constant [121] during pregnancy. The return to prepregnancy values of various echocardiographic parameters can be delayed; women evaluated six to eight weeks PP still showed residual enlargement of their cardiac chambers [121,122]. Complete resolution, however, was shown by four months postpartum [65].

Contractility

Using right heart catheterization and arterial line in a study limited to 36–38 weeks gestation, Clark *et al.* [75] reported no change in LV stroke work (the product of SV and systolic BP) compared with 12 week PP. They, however, did not report on myocardial performance in the first or second trimesters. Most recent data on systolic function in pregnancy, drawn from echocardiographic studies, have shown small and inconsistent changes. Using ejection fraction as a measure of systolic function, some of these trials reported

no change [58,83,121,126], while others reported either a decrease [127] or an increase [51,56,115]. The use of MRI in the CHIRP study showed no significant change in ejection fraction during the third trimester compared to four months PP [65]. A number of recent studies, which used speckle-tracking echocardiography to assess LV functional changes during normal pregnancy, also reported inconsistent results. Naqvi *et al.* reported an increase in cardiac contractility demonstrated by increased LV radial and longitudinal rate of deformation, especially during the first and second trimester [128]. Savu *et al.* [63] evaluated 51 women in each trimester and three to six months postpartum. Despite an increase in stroke work (which reflects global cardiac performance) throughout pregnancy, no significant change in ejection fraction and circumferential or radial strain was demonstrated, though a decrease in longitudinal strain during the third trimester was shown [63]. The authors concluded that the reduction in longitudinal strain did not necessarily represent systolic dysfunction but could be related to the increased heart rate and loading conditions in the third trimester [63]. Ando *et al.* [129] reported on a retrospective speckle tracking echocardiographic study in 74 normal pregnant women and 21 healthy age-matched female controls. These investigators found no change in myocardial mechanical function measured by global longitudinal strain, radial strain, circumferential strain, systolic and diastolic global longitudinal strain rate, global radial strain rate, and global circumferential strain rate, and concluded that despite heart remodeling, LV function remains unchanged. Cong *et al.* [130] used sequential two-dimensional echocardiography and 3D speckle tracking echocardiography in 68 pregnant women during each trimester of pregnancy and six to nine months PP, and 30 age-matched healthy controls. These investigators reported a significant decrease in global longitudinal strain, global circumferential strain, global area strain, and global radial strain in late pregnancy along with a small (5%) decrease in ejection fraction.

Information on RV function in pregnancy is limited. In the CHIRP study [65], no change in RV ejection fraction (62 ± 3 to 61 ± 3) was demonstrated. Savu *et al.* evaluated RV function using tissue Doppler strain rate imaging of the RV free wall and reported an increase in longitudinal strain rate in the first and second trimesters and a decrease in the third trimester [63].

Diastolic function

There have been a number of reports of changes in LV diastolic function during normal pregnancy with somewhat different results [121,122,131]. In an early study, Mesa *et al.* [121] conducted an echocardiographic evaluation at the end of each trimester in 37 healthy pregnant women (8 women were also followed 4–10 weeks). This study showed complex changes including an increase in early mitral inflow velocity (*E* wave) with a significantly increased *E*/*A* ratio in early pregnancy, and in contrast, a significant increase in late mitral inflow velocity (*A* wave) in the second and third trimesters. Additionally, an increase in pulmonary vein reverse (PVr) flow was demonstrated throughout pregnancy. While these changes might represent an impaired diastolic function, the ratio of *A* wave to PVr was preserved or even increased [121], implying that the observed changes were more likely due to an increase in plasma volume rather than a marker of diastolic dysfunction. Nevertheless, the increase in both *A* wave and PVr may represent a need for a more powerful atrial contraction to overcome a possible decrease in ventricular compliance in pregnancy secondary to increased LV mass. Moran *et al.* [131] also showed an early increase in *E* velocity, peaking at 18 weeks and returning to normal level during late pregnancy and an increase in *A* velocity and fall of the *E*/*A* ratio at 18 weeks remaining high throughout the rest of the pregnancy. Fok *et al.* [122] performed a prospective, longitudinal, observational study of tissue Doppler imaging in 35 healthy pregnant women These investigators showed that early diastolic myocardial velocities (E') peaked in the beginning of the second trimester and were subsequently decreased during the third trimester and PP, while late diastolic myocardial velocities (A') were found to be increased in the second trimester, but decreased again in third trimester and in the PP period. As a result, the often used marker of diastolic function, E/E' ratio, was shown to be decreased as pregnancy progressed, though it was maintained within a normal range [122].These investigators concluded that LV diastolic function was preserved during pregnancy and is augmented at late diastole to accommodate the increased preload. In the CHIRP study [65], the authors did not report on diastolic function with the use of MRI. However, echo findings showed an increase in late mitral inflow velocities (*A* wave) and a decrease in *E*/*A* ratio in the third trimester of pregnancy compared with postpartum [65].

Valvular regurgitation

A-single center echocardiographic study examined the prevalence of valvular regurgitation in 107 pregnant women, 55 of whom prior to 28 weeks gestation, compared to 51 age-matched non-pregnant controls [132]. Rates of tricuspid regurgitation (TR) was 42% in the control group and 67% in the pregnant group with a median peak regurgitant velocity of 1.7 ms. Pulmonic regurgitation (PR) increased from 50% in the control group to 96% at ≥28 weeks gestation with a median peak regurgitant velocity of 1.1 ms. Incidence of mitral and aortic regurgitation was 27% and 2% in the control group, respectively, and was not increased in the pregnancy group [132]. Similar findings were reported by Campos *et al.* in a study published one year later. These investigators evaluated 18 healthy pregnant women and 18 age-matched controls and demonstrated early and progressive dilatation of pulmonary, tricuspid, and mitral annuli during pregnancy [125], which was associated with progressive increase in valvular regurgitation. Forty-four percent of the control patients had TR and 39% had PR, but none had left-sided regurgitation. The prevalence of TR and PR increased as pregnancy progressed, and both reached 94%

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by 36–40 week gestation. Mitral regurgitation was demonstrated in 27% of participants in late pregnancy and none showed aortic regurgitation. By three to six weeks postpartum, mitral regurgitation resolved completely, while TR and PR were still more prevalent compared to the beginning of pregnancy [125].

Pericardial effusion

Haiat and Halphen [133] examined 123 women at various stages of pregnancy and reported pericardial effusion in 19/48 (40%) at ≥32-week gestation. All of them were asymptomatic, despite moderate-large effusion shown in 6/19 cases. Within four weeks postpartum, all effusions resolved [133]. Abduljabbar *et al.* [134] followed 52 women throughout pregnancy, and 11 of them were also examined at six-weeks postpartum. Pericardial effusion was found in 15%, 19%, and 44% of women in the first, second, and third trimester, respectively, and was more prevalent in first pregnancies and in women who gained more than 12 kg weight during their pregnancy. The effusions were resolved by six-weeks postpartum in all 11 patients who were reexamined PP [134].

Ventilation and gas exchange

Both oxygen consumption (VO_2) and carbon dioxide production (VCO_2) are increased in pregnancy [135,136], probably as a result of an increased metabolic rate in the pregnant woman and the increased metabolic demands of the growing fetus, and are 20–30% higher at term compared with baseline levels while the ratio of VCO_2/VO_2 is maintained [136,137]. Minute ventilation is increased from the beginning of pregnancy to a greater degree than VO_2 or VCO_2 [138,139], probably as a result of the effect of progesterone (and to a lesser degree, estradiol) on the brain-breathing center [140,141]. The increased awareness of many pregnant women to this elevated ventilatory drive contributes to the commonly reported "physiologic dyspnea of pregnancy."

Summary

Pregnancy is associated with a mark adaptation of the CV system with important changes in blood volume and hemodynamics during gestation, labor, delivery and the puerperium. These changes can represent a significant burden and a "stress test" to the patient with heart disease and limited cardiac reserve. With increased number of pregnant women with heart disease due to pregnancy at older age and increasing number of women with congenital heart disease surviving to childbearing age, more physicians are involved in the care of such women. A good understanding of the physiologic changes of pregnancy and their potential impact on both maternal and fetal outcome is critical.

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