

Cardiovascular Physiology of Pregnancy

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Pregnancy is a dynamic process associated with significant physiological changes in the cardiovascular system. These changes are mechanisms that the body has adapted to meet the increased metabolic demands of the mother and fetus and to ensure adequate uteroplacental circulation for fetal growth and development. Insufficient hemodynamic changes can result in maternal and fetal morbidity, as seen in preeclampsia and intrauterine growth retardation. In addition, maternal inability to adapt to these physiological changes can expose underlying, previously silent, cardiac pathology, which is why some call pregnancy nature's stress test. Indeed, cardiovascular disease in pregnancy is the leading cause of maternal mortality in North America.¹ We therefore review here the normal cardiovascular physiology of pregnancy to provide clinicians with a basis for understanding how the presence of cardiovascular disease may compromise the mother and fetus and how their decisions about medical care may need adjustment.

Maternal Hemodynamic Changes

Pregnancy is associated with vasodilation of the systemic vasculature and the maternal kidneys. The systemic vasodilation of pregnancy occurs as early as at 5 weeks and therefore precedes full placentation and the complete development of the uteroplacental circulation.² In the first trimester, there is a substantial decrease in peripheral vascular resistance, which decreases to a nadir during the middle of the second trimester with a subsequent plateau or slight increase for the remainder of the pregnancy³ (Figure 1). The decrease is $\approx 35\%$ to 40% of baseline. Systemic vascular resistance increases to near-pregnancy levels postpartum,⁴ and by 2 weeks after delivery, maternal hemodynamics have largely returned to nonpregnant levels.⁵ Increased vascular distensibility, or compliance, has been observed in normal human pregnancy starting in the first trimester.⁶ Systemic vascular resistance increases to near-pregnancy levels postpartum.⁴ Vasodilation of the kidneys results in a 50% increase in renal plasma flow and glomerular filtration rates by the end of the first trimester. This results in decreases in serum creatinine, urea, and uric acid values.⁷

Cardiac Output

Cardiac output increases throughout pregnancy.⁸ Invasive measuring techniques are rarely used during pregnancy, so echocardiography is most commonly used to assess hemodynamics in pregnancy. Cardiac output measurements are usually made with the mother in the left lateral decubitus position

to avoid positional variation. The sharpest rise in cardiac output occurs by the beginning of the first trimester, and there is a continued increase into the second trimester.⁹ After the second trimester, there is debate as to whether cardiac output increases, decreases, or plateaus. By 24 weeks, the increase in cardiac output can be up to 45% in a normal, singleton pregnancy.¹⁰

Echocardiography and cardiac magnetic resonance imaging estimates of cardiac output trend similarly in pregnancy. In a comparative study of 34 normal pregnant women with images taken in the third trimester and at least 3 months postpartum, both modalities demonstrated an increase in left ventricular end-diastolic volume, an increase in left ventricular mass, and an increase in cardiac output during pregnancy, but the values were consistently underestimated by transthoracic echocardiography.¹¹

Cardiac output in a twin pregnancy is 15% higher than that of a singleton pregnancy, and a significantly larger increase in left atrial diameter is seen, consistent with volume overload.¹⁰ Cardiac output early in gestation is thought to be mediated by the increase in stroke volume, whereas later in gestation, the increase is attributable to heart rate. Stroke volume increases gradually in pregnancy until the end of the second trimester and then remains constant or decreases late in pregnancy.

Blood Pressure

There is a decrease in arterial pressures, including systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure, and central SBP during pregnancy. DBP and mean arterial pressure decrease more than SBP during the pregnancy. Arterial pressures decrease to a nadir during the second trimester (dropping 5–10 mm Hg below baseline), but the majority of the decrease occurs early in pregnancy (6- to 8-week gestational age) compared with preconception values.³ Because many of these changes occur very early in pregnancy, they emphasize the importance of comparing hemodynamic measurements with preconception values rather than early pregnancy values when changes have already occurred. Arterial pressures begin to increase during the third trimester and return close to preconception levels postpartum. In a longitudinal study of blood pressure at 16 weeks postpartum, both brachial and central SBPs remained lower than preconception values but similar to early pregnancy levels.³ Although a decrease in blood pressure during pregnancy has been found in most studies¹² (Figure 2), a recent study challenged this

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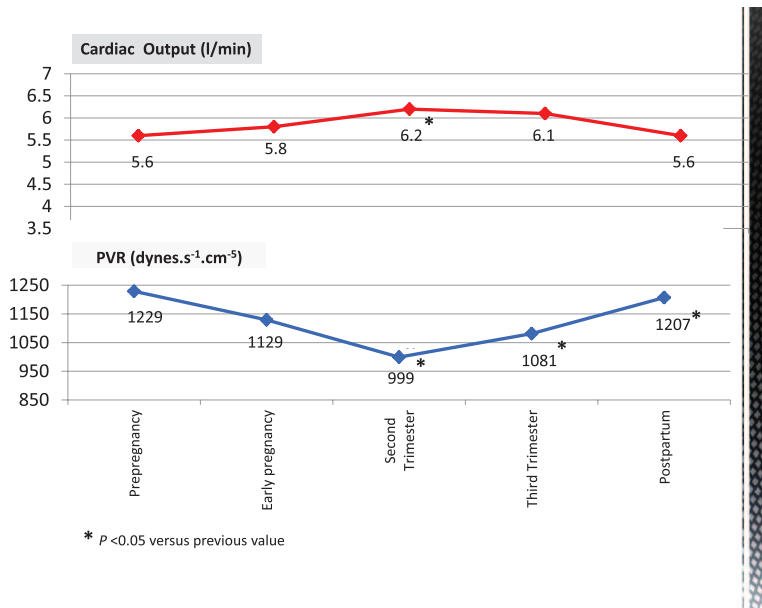


Figure 1. Detailed hemodynamics were longitudinally studied in 54 women with normal pregnancies preconception and then at 6, 23, and 33 weeks during pregnancy and 16 weeks postpartum. Radial artery waveforms were obtained with a high-fidelity micromanometer; a central waveform was generated with a validated central transfer function; and mean arterial pressure (MAP) was determined with integrated software. Cardiac output (CO) was assessed with a noninvasive, validated inert gas rebreathing technique, and peripheral vascular resistance (PVR) was calculated from the formula $PVR = MAP \text{ (mmHg)} \times 80 / CO \text{ (L/min)}$. The reciprocal relationship of CO and PVR in pregnancy is demonstrated. CO increases from preconception to the second trimester and then falls to the preconception level 16 weeks postpartum. The PVR fell significantly by the second trimester (a 19% fall), followed by an increase in the third trimester and a return to preconception levels by 16 weeks postpartum. Figure created from the data of Mahendru et al.³

“dogma” and demonstrated a progressive increase in blood pressure throughout gestation.¹³ Women with a body mass index >25 kg/m² before pregnancy have been shown by some to have significantly higher SBP, DBP, and mean arterial pressure (measured by an automated oscillometric device) at any point during the pregnancy and postpartum than women with lower body mass.¹² In a population-based cohort study (The Generation R Study), with blood pressure measured by an automated digital oscillometric sphygmomanometer, obese and overweight women had a higher blood pressure in the first trimester than normal-weight women, and this difference was sustained throughout pregnancy.¹⁴ Others have shown no difference in hemodynamic changes based on weight before pregnancy or total weight gain during pregnancy. The differing methods of assessing blood pressure in these studies (automated oscillometric devices versus finger arterial pressure based on the volume clamp method)¹⁵ may contribute to

the variations in the data, and importantly, largely unexplained but substantial ethnic differences exist in blood pressure levels observed during pregnancy and the risk of gestational hypertension.¹⁶

Heart Rate

Heart rate increases during normal gestation. Unlike many of the prior parameters that reach their maximum change during the second trimester, heart rate increases progressively throughout the pregnancy by 10 to 20 bpm, reaching a maximum heart rate in the third trimester. The overall change in heart rate represents a 20% to 25% increase over baseline.^{3,4,12,17}

Contractility

Although multiple cardiovascular parameters are altered during pregnancy, myocardial contractility⁶ and left ventricular

Serial Blood Pressures before, during and after pregnancy

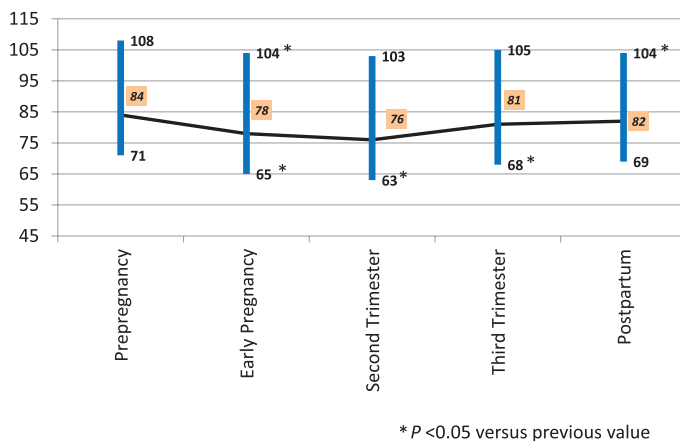


Figure 2. Detailed hemodynamics were studied longitudinally in 54 women with normal pregnancies before conception and then at 6, 23, and 33 weeks during pregnancy and 16 weeks postpartum. Blood pressures were measured in the nondominant arm with a validated automated measuring device. Blood pressure reached a nadir in the second trimester, although the majority of the reduction occurred early in pregnancy, followed by an increase in the third trimester and postpartum period. Systolic, diastolic, and mean arterial blood pressures are displayed. Significant differences are noted. Figure created from the data of Mahendru et al.³

and right ventricular ejection fractions do not appear to change during pregnancy.¹¹

Sympathetic Activity and Baroreceptors

During a normal pregnancy, vasomotor sympathetic activity is increased,¹⁸ and this increase occurs very early in pregnancy.¹⁹ It is postulated that when sympathetic activity is excessive, then gestational hypertension or preeclampsia may ensue.²⁰ Normal pregnancy appears to be associated with increased maternal baroreceptor sensitivity and an attenuated responsiveness to α -adrenergic stimulation.²¹ In pregnant rats, decreased pressor responsiveness to angiotensin II, norepinephrine, and vasopressin has been observed, and this is improved with inhibition of prostaglandin production.²² In pregnant patients, resistance to the pressor effects of infused angiotensin II has been demonstrated as early as the 10th week of pregnancy.²³

Pregnancy Hormonal Changes

There is a relationship between increased levels of estrogen and progesterone and vasodilation,²⁴ and certainly, levels of both rise substantially during pregnancy. Relaxin is a peptide hormone produced by the corpus luteum that circulates during pregnancy. It is detectable in the luteal phase of the ovulatory cycle. If conception occurs, serum concentrations rise to a peak at the end of the first trimester and fall to an intermediate value throughout pregnancy.²⁵ This hormone has been demonstrated to have an endothelium-dependent vasodilatory role in pregnancy that can influence small arterial resistance vessels.²⁶ In a Swedish observational study of pregnant women, the effects of serum concentrations of progesterone, relaxin, and estradiol on arterial blood pressure were studied. Higher serum concentrations of relaxin and progesterone early in pregnancy were related to lower mean SBPs in the second and third trimesters. Furthermore, those women with DBPs >90 mmHg late in pregnancy had lower relaxin concentrations earlier in pregnancy compared with those with lower DBPs.²⁷ Nitric oxide is important in the physiology of the reproductive

system²⁸; however, its role in mediating the systemic vasodilation seen in human pregnancy is uncertain, with studies of human hand flow suggesting that it does play a role²⁹ and studies of forearm flow suggesting that it does not.³⁰ In pregnant animals, prostacyclin appears to be produced in sufficient quantity to play a role in vasodilation.³¹

Renin-Angiotensin-Aldosterone System

In a normal pregnancy, there is substantial activation of the renin-angiotensin-aldosterone system. The enhanced activity of the renin-angiotensin and aldosterone systems occurs early in pregnancy, with increases in plasma volume starting at 6 to 8 weeks and rising progressively until 28 to 30 weeks. During pregnancy, as estrogen production increases, so does renin substrate (angiotensinogen) production; thus, angiotensin levels increase throughout pregnancy.^{32,33} This activation maintains blood pressure and helps retain salt and water in pregnancy as maternal systemic and renal arterial dilation (with resulting salt and water loss) creates an "underfilled" cardiovascular system. In the second and third trimesters, there is an increase in exchangeable sodium of ≈ 500 mEq (≈ 20 mmol/wk)³⁴ and a net gain of ≈ 1000 mg.⁷ Furthermore, during pregnancy, relaxin stimulates increased vasopressin secretion and drinking, resulting in increased water retention. Despite increases in exchangeable sodium, plasma osmolality is reduced and the hyponatremic hypervolemia of pregnancy ensues³⁵ (Table). Progesterone is a potent aldosterone antagonist that acts on the mineralocorticoid receptor to prevent sodium retention³⁶ and to protect against hypokalemia.⁷ The importance of aldosterone is evident in preeclampsia in which plasma volume is reduced and aldosterone concentrations are low. Activation of the mineralocorticoid receptor by maternal aldosterone appears to be required for trophoblast growth and normal fetoplacental function.³⁷ Maternal plasma atrial natriuretic peptide levels increase by 40% in the third trimester and are 1½ times normal in the first week postpartum, suggesting a significant role in postpartum diuresis.³⁸

Table. Interrelationships of Changes in the Major Variables That Contribute to the Cardiovascular Changes in Pregnancy Compared With Preconception Values

Preconception		Pregnancy			
Baseline		First Trimester	Second Trimester	Third Trimester	Labor
Hemodynamic	CO	↑	↑↑	↑↑	↑↑↑↑
	SVR	↓	↓↓	↓↓	
	HR	↑	↑↑	↑↑↑	↑↑↑↑
	BP	↓	↓	↔	(Pain)
Neurohumoral		↑ Sympathetic activity			
		↑ Estrogen/progesterone/relaxin			
Renin/angiotensin	Plasma volume*	↑↑	↑↑↑	↑↑↑↑	↑↑↑↑↑
RBC changes	RBC mass	↑	↑↑	↑↑	(Autotransfusion)
Structural changes	LV wall mass	↑	↑	↑	
	Chamber sizes	4-Chamber enlargement			
	Aorta	Increased distensibility			

BP indicates blood pressure; CO, cardiac output; HR, heart rate; LV, left ventricular; RBC, red blood cell; and SVR systemic vascular resistance. ↑ and ↓ reflect relative changes in parameters from preconception values.

*The greater increase in plasma volume relative to the increase in RBC mass results in the physiological anemia of pregnancy.

Changes in Plasma Volume and Red Blood Cell Mass

There are significant increases in total blood volume, plasma volume, and red blood cell mass during pregnancy.^{39,40} In pregnancy, erythropoiesis is increased, provided that the mother has normal nutrition and sufficient iron and vitamin supplements.⁴¹ Placental lactogen may enhance the effect of erythropoietin on erythropoiesis. Maternal erythropoietin production is enhanced in normal pregnancy and when red cell hemoglobin content is lower and subclinical iron deficiency exists.⁴² Erythrocyte life span is decreased during normal pregnancy as a result of “emergency hemopoiesis” in response to elevated erythropoietin levels.⁴³ There is a direct association between plasma volume expansion and fetal growth, and reduced plasma volume expansion has been associated with preeclampsia and other pathological conditions. Blood volume increases significantly within the first few weeks of gestation and increases progressively throughout the pregnancy. The total blood volume increase varies from 20% to 100% above prepregnancy levels, usually close to 45%. In addition to plasma volume expansion, there is an increase in red blood cell production up to 40% via erythropoiesis. Plasma volume increases proportionally more than the red blood cell mass, resulting in a “physiological anemia” from hemodilution, with hemoglobin levels as low as 11 g/dL considered physiological.

Remodeling

Left ventricular wall thickness and left ventricular wall mass increase by 28% and 52% above prepregnancy values, respectively, throughout pregnancy.⁵ Recent cardiac magnetic resonance imaging studies quantify a 40% increase in right ventricular mass.¹¹ Studies in pregnant mice suggest that the temporary cardiac remodeling, associated with volume overload and ventricular hypertrophy is accompanied by upregulation of vascular endothelial growth factor and increased myocardial angiogenesis with no increase in cardiac fibrosis.⁴⁴ In keeping with vasodilation of the systemic vasculature during pregnancy, increased vascular distensibility occurs,⁶ and the aortic augmentation index, a marker of aortic stiffness, decreases significantly early during pregnancy, reaching a nadir in the second trimester and gradually increasing in the third trimester.^{3,45} Four months after delivery, this marker of aortic stiffness remains higher than preconception measurements. This may not be sustained, although higher baseline levels of this measure of aortic stiffness have been observed in multiparous women compared with nulliparous women

Transthoracic Echocardiography and Cardiovascular Magnetic Resonance

Typical transthoracic echocardiographic findings in a normal pregnancy include mild 4-chamber dilatation (changes in the right atrium and ventricle are typically greater than in the left atrium and ventricle) with transient, trivial mitral regurgitation and physiological tricuspid and pulmonary regurgitation. Aortic regurgitation is not seen in a normal pregnancy.⁴⁶ Echocardiography is the most common imaging technique used in pregnancy, but it has some limitations, including observer variability in interpretation and poor image quality

in some women. Cardiovascular magnetic resonance use in pregnancy is safe for the mother and fetus⁴⁷ and assesses left ventricular volumes better.⁴⁸ Furthermore, left ventricular mass, cardiac output, and stroke volume are underestimated by echocardiography compared with cardiovascular magnetic resonance.¹¹ Finally, assessment by cardiovascular magnetic resonance of the atria, right ventricle, and aorta in pregnant patients with suspected cardiovascular abnormalities is probably more accurate than echocardiography and should be considered on a case-by-case basis.¹¹

Labor and Delivery

The maximum cardiac output associated with pregnancy occurs during labor and immediately after delivery, with increases of 60% to 80% above levels seen before the onset of labor. This is related to many factors, including increasing heart rate and preload associated with the pain of uterine contractions, increases in circulating catecholamines,⁴⁹ and the autotransfusion of 300 to 500 mL blood from the uterus into the systemic circulation immediately after each contraction. Other factors, including positional changes (supine versus left lateral recumbent position) and blood loss, influence hemodynamic changes in individual patients.

Spinal anesthesia is commonly used for caesarean section and can lead to major secondary cardiovascular effects. The most frequent cardiovascular response to spinal anesthesia for elective caesarean section is a marked decrease in systemic vascular resistance and compensatory increases in heart rate and stroke volume.⁵⁰ In a review of randomized, controlled trials of spinal anesthesia and caesarean section, the administration of prophylactic intravenous phenylephrine before delivery reduced the risk of hypotension by 64% compared with placebo and after delivery reduced the risks of hypotension, nausea, and vomiting by a similar amount.⁵¹ In recent years, phenylephrine rather than ephedrine has become the vasopressor of choice in obstetrics.⁵²

Clinical Cardiovascular Findings in Normal Pregnancy

During pregnancy, healthy women experience some increased shortness of breath on exertion and increased fatigue. Because resting cardiac output is increased in pregnancy, the maximal cardiac output induced by exercise is achieved at a lower level of work. During rest or weight-bearing exercise (eg, walking or treadmill exercise), maternal oxygen uptake is significantly increased compared with the nonpregnant state.⁵³ Furthermore, resting minute ventilation and tidal volume are increased and the expiratory reserve volume and functional residual capacity are decreased in pregnancy.^{54,55} Under the influence of neurohormonal changes, plasma volume increases more than red blood cell mass, resulting in the “physiological anemia” of pregnancy, and increased vasopressin secretion and drinking result in increased water retention, so despite increases in exchangeable sodium and a net gain of ≈ 1000 mg sodium, plasma osmolality is reduced and the hyponatremic hypervolemia of pregnancy occurs (Table). As a result, gestation-dependent edema can be found in up to 80% of healthy pregnant women. With the increases in maternal heart rate and

cardiac output and the associated hypervolemia, the substantially reduced peripheral vascular resistance, and the evolving echocardiographic mild 4-chamber dilation of the heart in pregnancy, there are changes in heart sounds. After the first trimester, in the majority of mothers, the first sound is louder and has an exaggerated split (resulting from early mitral closure), an ejection systolic flow murmur is detected in 90%, a third heart sound is detected in 80%, and an atrioventricular diastolic flow murmur is detected in 20%.⁵⁶ ECG changes in a normal pregnancy reflect the increased heart rate with minor left or right shifts in the QRS axis but no significant changes in ECG time intervals.¹⁷

Summary

The cardiovascular system undergoes significant structural and hemodynamic changes during the course of pregnancy. There are major increases in cardiac output and a decrease in maternal systemic vascular resistance; the renin-angiotensin-aldosterone system is significantly activated; and the heart and vasculature undergo remodeling. These adaptations allow adequate fetal growth and development, and maladaptation has been associated with fetal morbidity. Understanding the normal cardiovascular changes in pregnancy is essential to caring for patients with cardiovascular disease.

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