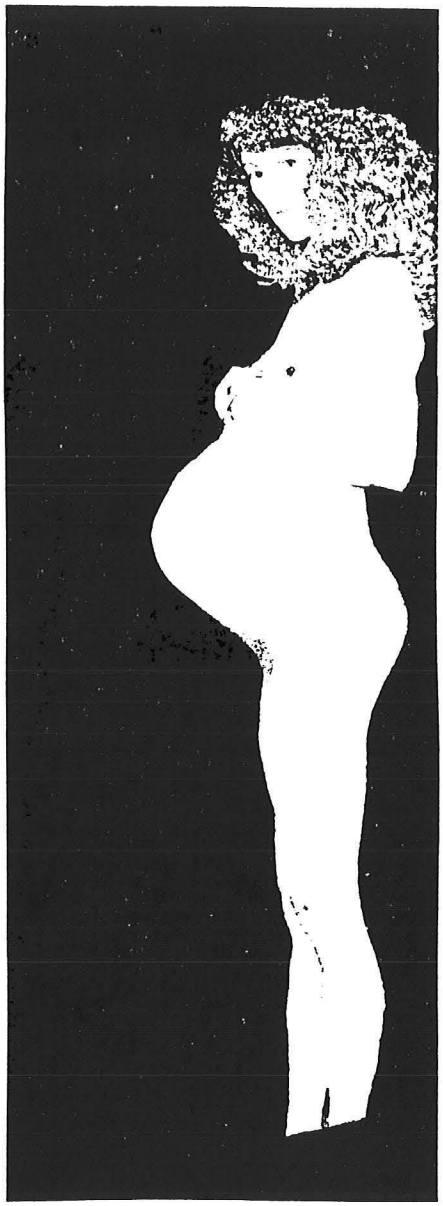
PULMONARY DISORDERS IN PREGNANCY



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PULMONARY DISORDERS IN PREGNANCY

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PULMONARY DISORDERS IN PREGNANCY

Women during child bearing years frequently regard their obstetrician as their primary care physician even when not pregnant. Nevertheless, it is common for internists and all of the subspecialists of Internal Medicine to see and treat women during pregnancy. It is therefore important for us to know the adaptations that occur in the cardiopulmonary system during pregnancy, the symptoms that may arise due to these changes in the absence of cardiopulmonary diseases, and the appropriate use of drugs in pregnant women. This review will address these considerations and will then discuss the diagnosis and therapy of the leading cause of death encountered in pregnant women.

RESPIRATORY CHANGES DURING NORMAL PREGNANCY

Upper Respiratory Tract

Table 1

Upper Respiratory Tract Changes
During Normal Pregnancy

Mucosal	Mucous glands
Hyperemia	Hyperplasia
Hypersecretion	Hypersecretion
Edema	
Nasal/sinus polyps	

Symptoms
- Nasal obstruction
- Sneezing
- Epistaxis

Camann, et al: Int Anesthesiol Clin 28:2-10, 1990; Paparella, et al: Otolaryngology, pp 1892-93, 1991.

Many pregnant women develop upper respiratory tract changes during normal pregnancy. The mucosal changes include hyperemia, hypersecretion, edema, and perhaps nasal or sinus polyps. In addition, the mucus glands become hyperplastic and are hypersecretory. These changes lead to nasal obstruction and sneezing interpreted by the patient as a chronic "head cold" (1). Additionally, epistaxis is common and sometimes profuse. Estrogen causes the alterations by increasing hyaluronic acid in the ground substance leading to hydration, edema and glandular changes (2).

These changes become extremely important in the pregnant patients who require intubation for a variety of indications. Physicians inserting endotracheal or gastric tubes either orally but particularly by the nasal route should use more lubrication than usual to prevent episodes of massive epistaxis. If nasal tracheal intubation is attempted it may not be possible to pass a tube larger than 6.0 mm (3).

These same lesions may be present in the tracheobronchial tree (4). The false vocal cords and the aryteniod region of the larynx appear swollen and inflamed in up to 75% of all pregnant women, and the edema may cause voice changes. These tracheobronchial changes further add to difficulty in performing endotracheal intubation (5).

Respiratory Muscles and Thorax

Table 2

Respiratory Muscle and Thorax Changes
During Normal Pregnancy

Enlarging uterus → Increased abdominal pressure
- Less abdominal muscle tone
- Upward displacement of diaphragm by about 4 cm
- No diaphragmatic impairment
- Normal PI max, PDI max

Thorax enlarges
- AP and transverse diameters each increase about 2 cm
- Subcostal angle broadens (68.5° to 103.5°)
- Thoracic circumference increases 5-7 cm

Gilroy, et al: Am Rev Respir Dis 137:668-672, 1988; Contreras, et al: Am Rev Respir Dis 144:837-841, 1991.

During pregnancy the enlarging uterus progressively increases the intraabdominal pressure. Part of this increase is mitigated by less active tone of the abdominal muscles allowing a larger abdominal cavity (6). Additionally, the diaphragm is displaced upward into the thoracic cavity by up to 4 cm. Nevertheless, diaphragmatic function is not impaired as indicated by a normal maximal inspiratory force at the mouth, PI max, and normal maximal inspiratory pressures across the diaphragm, PDI max (7, 8). In fact, diaphragmatic excursions during quiet breathing in pregnant women are larger than that in the absence of pregnancy suggesting that inspiration during pregnancy tends

to be even more due to diaphragmatic contraction than when not pregnant (9, 10).

The lower thorax enlarges by about 2 cm in both the anteroposterior and transverse diameters. The subcostal angle progressively broadens from about 68.5° to 103.5° (11). These changes cause an increase in the chest circumference by about 5 to 7 cm. The change in the subcostal angle is secondary to relaxation of the ligamentous attachments of the ribs and is not directly due to the mechanical effects of the enlarging uterus (11).

Thus, although the lung looks small on a chest x-ray due to the decreased apex to diaphragm distance, the volume is actually about normal due to the enlarged thorax. All of these changes, with the exception of those of the subcostal angle, return to normal after delivery (8).

Table 3

Static Lung Volumes During Normal Pregnancy

Residual volume decreases 7% to 22% below the nonpregnant value
Expiratory reserve volume decreases 8% to 40%
Functional residual capacity decreases 10%-25% after 5th-6th month
Inspiratory capacity increases significantly
Therefore total lung capacity and vital capacity remain normal

Cugell, et al: Am Rev Tuberc 67:568-597, 1953; Rubin, et al: Am J Obstet Gynecol 72:963-969, 1956.

Because of the high diaphragm there is a progressive decrease in the amount of air left in the lung after a maximal exhalation; i.e. the residual volume (RV), decreases from 7% to 22% below the nonpregnant value. Similarly, the amount of air that can be exhaled below the resting end expiratory lung volume, the expiratory reserve volume (ERV), decreases 8% to 40%. Thus, after the fifth to sixth month of pregnancy the amount of gas in the lungs at the end of a normal expiration, the functional residual capacity (FRC), decreases 10% to 25% (9, 12-16). However, due to the enlarged thoracic cavity the amount of gas that the patient is capable of inspiring above FRC, the inspiratory capacity (IC), increases significantly. Consequently, the total lung capacity (TLC) and the vital capacity (VC) remain normal.

Static lung volumes such as TLC, RV, ERV and FRC are not usually measured when studying patients with lung disease either in the pregnant or nonpregnant state. The standard pulmonary function tests used in all patient management are indicated in Table 4.

Pulmonary Function Tests

Table 4

Standard Pulmonary Function Tests
During Normal Pregnancy

Forced vital capacity (FVC)	Normal
Forced expiratory volume in 1 sec (FEV_1)	Normal
Forced expiratory flow 25-75% (FEF_{25-75})	Normal
Peak expiratory flow rate (PEFR)	Normal
Diffusion capacity (DL_{CO})	Slight increase to decrease

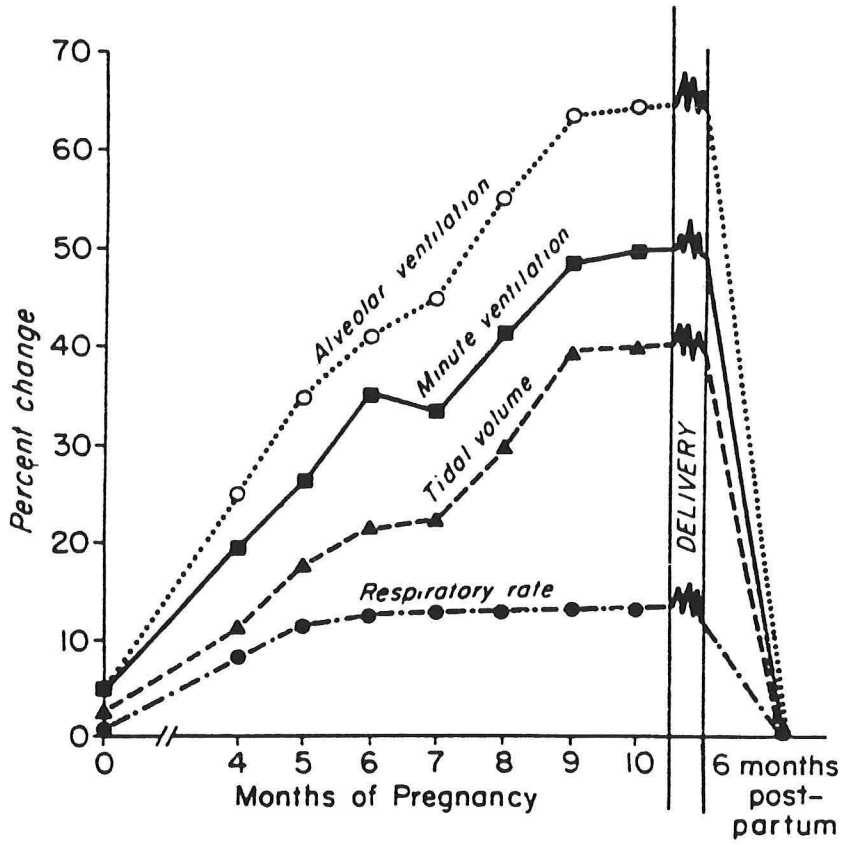
Cugell, et al: Am Rev Tuberc 67:568-597, 1953; Milne, et al: Br J Obstet Gynaecol 84:448-451, 1977.

As indicated in this table, the forced vital capacity, forced expiratory volume in 1 sec, ratio of FEV_1/FVC, the forced expiratory flow 25-75%, and the peak expiratory flow rate are all the same in pregnant as compared to nonpregnant women (14, 17, 18). The diffusion capacity either shows no change or is slightly increased early in pregnancy and slightly decreased late in pregnancy (19). Thus, no special prediction values or conversion factors are necessary for interpreting the results of standard pulmonary function tests in pregnant women.

Ventilation

Figure 1

Ventilation During Normal Pregnancy



Bonica, J.J.: In: Parturition and Perinatology, pp. 2-19, 1973.

Perhaps the most interesting change in pulmonary function is an increase in ventilation that begins in the first trimester and progresses until near time of delivery (8, 12, 20). The total amount of gas moved in and out of the lungs per minute, the minute ventilation, is about 50% larger at term than the minute ventilation of a nonpregnant woman. Most of this increase is due to a 40% increase in the size of each tidal volume with only a modest increase in the respiratory rate. Thus, the alveolar ventilation increases up to 70% above that of the nonpregnant woman due to the increase in tidal volume with no change in dead space ventilation. Concurrently there is an increase in the oxygen consumption and carbon dioxide excretion due to fetal and maternal tissue growth, but the increase is only about 21%. Thus there is significant, protracted hyperventilation (21).

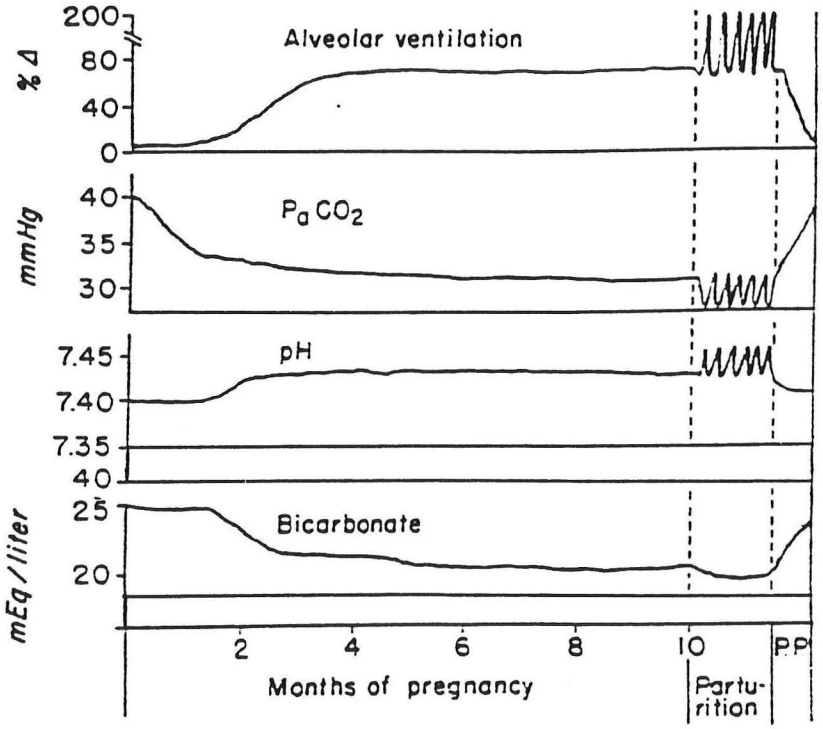
Hyperventilation continues during exercise, since the minute ventilation of exercising pregnant women is about 38% higher than that of nonpregnant control subjects (22, 23).

Progesterone blood concentrations increase gradually during pregnancy from 25 ng/ml in the first trimester to 150 ng/ml near term. Progesterone is a known respiratory center stimulant both increasing resting minute ventilation and altering the response of the respiratory center to $PaCO_2$ (8). Estrogen may have some additional effect (19).

Arterial Blood Gases

Figure 2

Arterial Blood Gas Values During Normal Pregnancy



Bonica, J.J.: In: Parturition and Perinatology, pp. 2-19, 1973.

The effect of the increased alveolar ventilation during pregnancy on the $PaCO_2$ is indicated in the second panel of Figure 2. After a rapid drop in the first trimester, there is only a modest change for the remainder of the pregnancy so that the $PaCO_2$ is approximately 32 mm Hg for several months. As would be

expected, the chronic respiratory alkalosis of pregnancy is compensated by increased renal bicarbonate excretion; the bicarbonate concentration is usually between 18 and 21 mEq/L (22, 24-26). This level of bicarbonate maintains a pH of 7.40 to 7.45 (22, 24, 27, 28). During labor and delivery, this change may be accentuated by the patient with superimposed acute hyperventilation, and the pH may increase to 7.6 or above, an alkalosis potentially harmful to the baby.

Table 5

The Effect of Hyperventilation on the Alveolar (P_AO_2) and Arterial Oxygen Tensions (PaO_2)

The Alveolar Air Equation

$$P_AO_2 = F_IO_2 \ (P_B - P_{H_2O}) - \frac{PaCO_2}{R.Q.}$$

$$\text{Usual } P_AO_2 = 0.21 \ (760 - 47) - \frac{40}{0.8} = 100 \text{ mm Hg}$$

$$\text{Pregnant } P_AO_2 = 150 - \frac{32}{0.8} = 110 \text{ mm Hg}$$

Normal $(P_AO_2 - PaO_2) = \leq 10$ mm Hg

Usual $PaO_2 \geq 90$ mm Hg

Pregnant $PaO_2 \geq 100$ mm Hg

The effect of hyperventilation on the alveolar and arterial oxygen tensions may be estimated by the alveolar air equation in association with the alveolar-arterial oxygen relationship (P_AO_2-PaO_2). The mean P_AO_2 may be estimated by multiplying the fraction of inspired oxygen times the barometric pressure minus water vapor pressure and subtracting from this the $PaCO_2$ divided by the respiratory quotient. Under usual eucapnic conditions the alveolar oxygen tension is approximately 100 mm Hg. Under the conditions of chronic hyperventilation, encountered in the pregnant patient, the P_AO_2 increases by a little more than the $PaCO_2$ is reduced. In the example in Table 5 the estimated P_AO_2 of a pregnant patient with a $PaCO_2$ of 32 is about 110 mm Hg.

In the presence of normal lungs the (P_AO_2-PaO_2) gradient is 10 mm Hg or less. If this relationship holds, pregnant patients would be expected to have a PaO_2 greater than that of a nonpregnant normal women.

Table 6

Arterial Blood Gas Values During Normal Pregnancy

Variable		Trimester of Gestation 1st	2nd	3rd
PaO_2	(mm Hg)	107.7 ± 8.5	107.0 ± 8.6	104.0 ± 6.2
$PaCO_2$	(mm Hg)	31.9 ± 1.2	32.9 ± 1.7	31.7 ± 2.3
pH	(units)	7.40 ± 0.007	7.40 ± 0.007	7.41 ± 0.013

Andersen, et al: J Obstet Gynaecol Br Commonw 76:16, 1969.

The arterial blood gas values during the normal pregnancy of about 25 women reported by Andersen are indicated in Table 6 (29) and are similar to those in some other reports. The data for $PaCO_2$ and pH confirm the studies already discussed. The mean values for PaO_2 are higher than would be expected in normal, nonpregnant women, although no controls were reported. Thus, these data tend to confirm the findings predicted by the alveolar air equation.

Table 7

Changes in Oxygenation with Posture in Normal Pregnant Women Near Term

	Sitting		Supine	
	PaO_2 mm Hg	(A-a O_2)	PaO_2 mm Hg	(A-a O_2)
$\bar{M}$ ± SD	101.2 ± 7.0	14.3 ± 6.0	94.6 ± 8.8	20.0 ± 8.9
Range	82 - 109	3.7 - 28	75 - 107	4.2 - 35

Awe, et al: Obstet Gynecol 53:182-185, 1979.

However, other studies disagree and have found that pregnant women often have mild hypoxemia and an increase in the (A-a O_2) gradient especially when recumbent (30, 31).

As reported in Table 7, Awe and his colleagues found that the (A-a O_2) difference was larger than 10 mm Hg among 70% of the sitting pregnant women whom they studied near term, although only one clearly had mild hypoxemia (31). When the same patients assumed a supine position, 83% had a widened (A-a O_2) gradient and five had PaO_2 values less than 90 mm Hg.

Investigations into the cause of an enlarged (A-a O_2) difference in late pregnancy have centered around the phenomenon

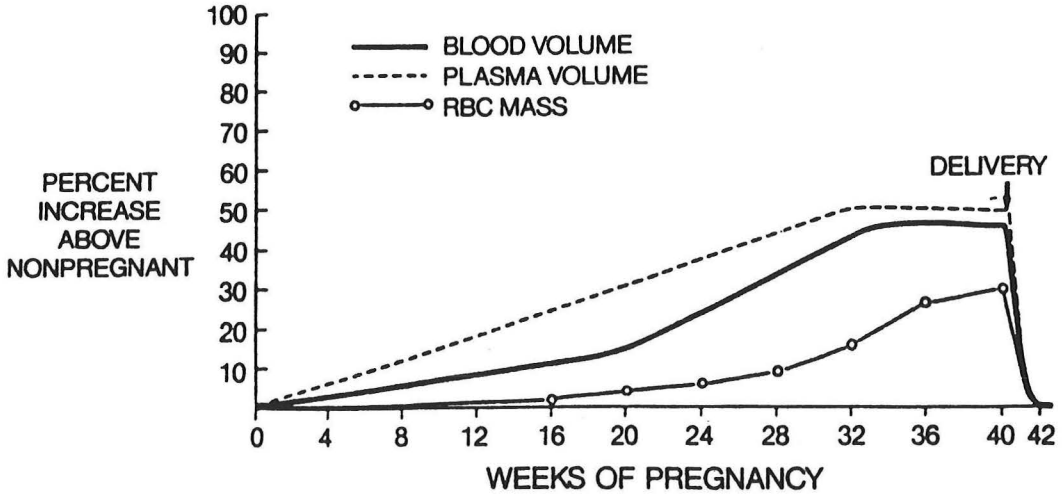
of "closing volume" (13, 31-34). As a person exhales towards residual volume small airways in the base of the lung may close due to the positive exhalation pressure. The lung supplied by each of these small airways does not empty completely, and on the ensuing inspiration the distribution of inhaled gas is altered. The closing volume is usually expressed as a percent of the vital capacity. If closing volume is less than the end-expiratory lung volume, the FRC, the phenomenon of airway closure does not occur. However, if the airways close above FRC, the potential consequence of airway closure is a decrease in ventilation to involved areas. This creates regions with low ventilation-perfusion ratios which may adversely affect gas exchange and result in arterial hypoxemia. Most studies suggest that airway closure during late pregnancy occurs closer to FRC than in the nonpregnant patient. The major reason for this is the decrease in FRC and in expiratory reserve volume as previously discussed. Regardless of the explanation it is important to realize that pregnant women with normal lungs may have an increase in the (P_A-Pa O_2) gradient and may have mild hypoxemia. These findings are particularly likely to occur in the third trimester of pregnancy.

CARDIOVASCULAR CHANGES DURING NORMAL PREGNANCY

Vascular

Figure 3

Increased Blood Volume During Normal Pregnancy



Scott, A.E.: Obstet Gynecol Annu 1:219, 1972.

The most striking effect of pregnancy on the cardiovascular system is a progressive increase in blood volume (35-39). The increase may start as early as the sixth week and accelerates rapidly until mid-term. Plateaus usually occur in the last trimester at a maximal value of 40% to 50% above the nonpregnant state. In some women there is a gradual increase during the plateau, whereas in others it apparently remains stable. The total increase in blood volume is approximately 1600 ml (36, 39, 40, 41). Extracellular fluid likewise increases by 1000 or 2000 ml. The increase in ECF and the mechanical obstruction of the inferior vena cava by the uterus result in peripheral edema which is seen in 50% to 80% of normal pregnancies (42, 43).

As indicated in the figure, the increase in blood volume is predominantly due to an increase in plasma volume, especially during the first and middle trimesters. There have been two theories advanced to explain the expansion of plasma volume.

Table 8

Theories of the Cause of the Increased Plasma Volume During Normal Pregnancy

Overfill:	Volume overload caused by primary gestational hypersecretion of aldosterone
Underfill:	Reduced effective blood volume with secondary hyperaldosteronism

The overfill theory suggests that pregnancy is a state of volume overload caused by primary gestational hypersecretion of aldosterone (38, 44). Proponents believe that estrogen induces an increase in renin that results in excess aldosterone production and sodium-fluid retention (38). Nonrenal renin is also produced by the uterus and liver during pregnancy and may contribute to fluid retention (45). Atrial natriuretic factor has also been suggested to play a role in the increased plasma volume (45).

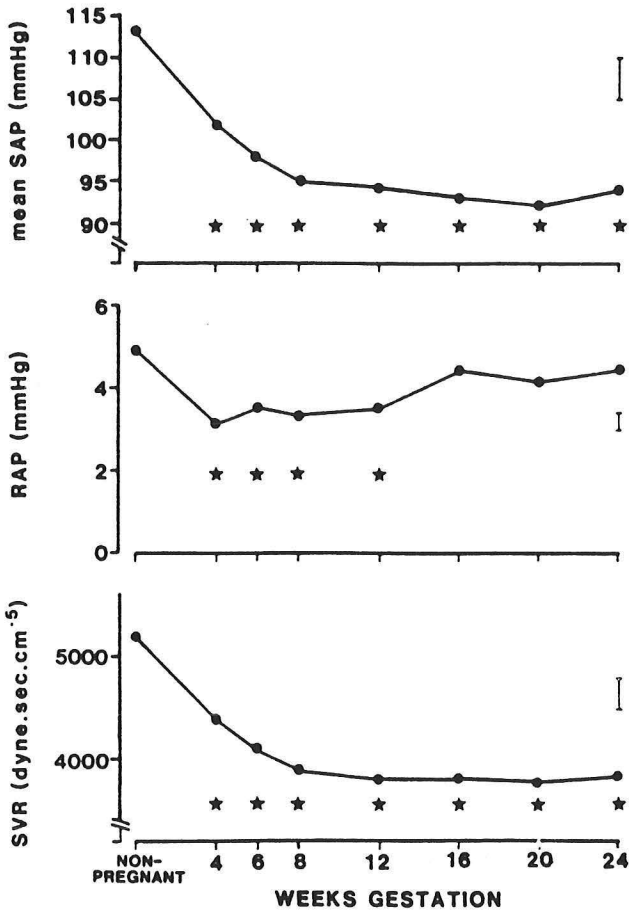
The overfill theory has been criticized for being unable to explain the fact that normal pregnant women have lower blood pressure in the first trimester than when not pregnant. However, more direct evidence has not been possible, since it is not feasible to make the appropriate measurements repeatedly in pregnant women.

The underfill theory suggests that there is actually a reduced effective blood volume due to vasodilitation with secondary hyperaldosteronism (46, 47).

Recent studies by Phippard and colleagues during eight baboon pregnancies have strongly suggested that the underfill theory is correct (47).

Figure 4

Circulatory Changes During Normal Pregnancy in Baboons



Phippard, et al: J Hypertens 4:773-779, 1986.

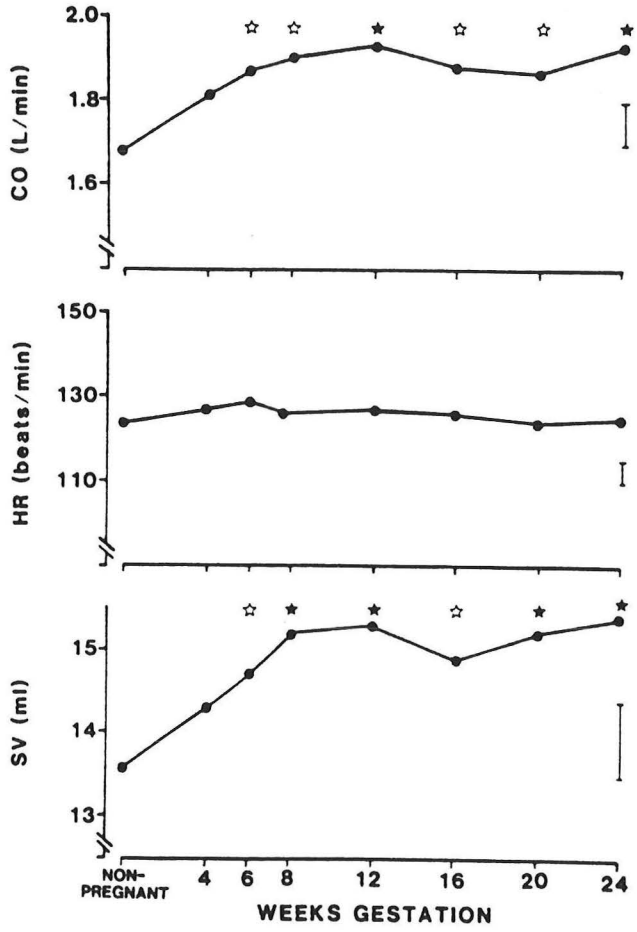
In these studies the investigators measured cardiovascular, blood volume and hormonal changes at four week intervals throughout pregnancy. Their data are reported as changes from the nonpregnant values on the left to time of delivery on the right with the change in the measured parameter recorded on the vertical axis and weeks of gestation on the horizontal axis. A star next to a datum point indicates a statistically significant change from nonpregnant values.

Figure 4 reports the mean systemic arterial pressure, the right atrial pressure, and the systemic vascular resistance calculated in the usual manner. The data indicate a significant

fall in mean arterial blood pressure and systemic vascular resistance which are progressive during the fourth, sixth and eighth week of gestation. There is an early fall in mean right atrial pressure beginning at the fourth week which is not progressive.

Figure 5

Circulatory Changes During Normal Pregnancy in Baboons

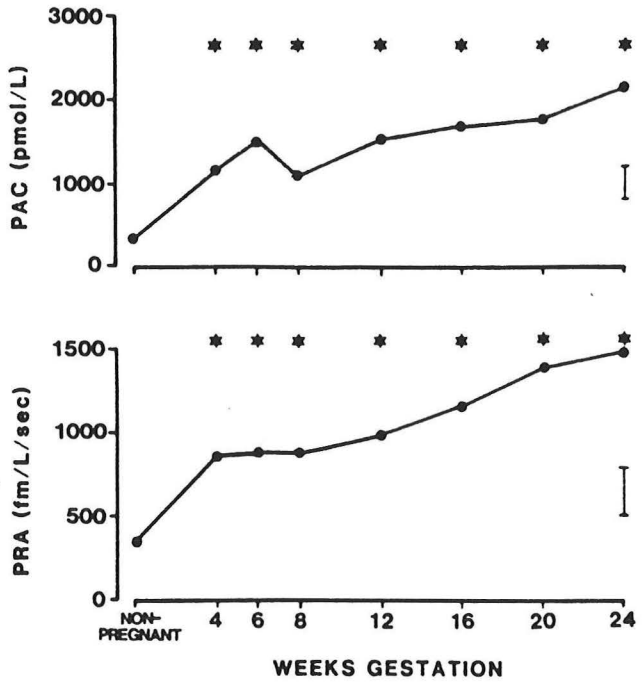


Phippard, et al: J Hypertens 4:773-779, 1986.

As indicated in Figure 5, there is a simultaneous increase in cardiac output which becomes significant at the sixth week and remains elevated during the remainder of the pregnancy. The increase in cardiac output is due to an increase in stroke volume with no significant change in heart rate.

Figure 6

Changes in Blood Aldosterone and Renin During Normal Pregnancy in Baboons

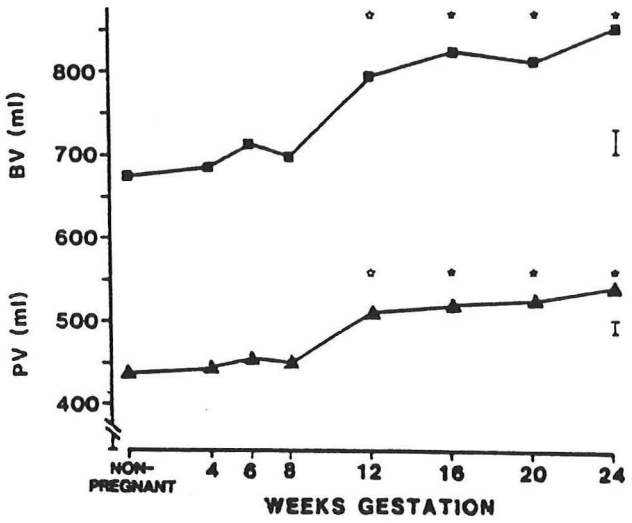


Phippard, et al: J Hypertens 4:773-779, 1986.

As indicated in Figure 6 there is a significant increase in plasma aldosterone concentration and plasma renin activity which also begins in the fourth week and progresses throughout the gestation.

Figure 7

Changes in Whole Blood and Plasma Volumes
During Normal Pregnancy in Baboons



Phippard, et al: J Hypertens 4:773-779, 1986.

However, as indicated in Figure 7, there is no significant increase in the blood or plasma volume until the twelfth week of gestation. Taken together, these changes strongly suggest that the primary event is a decrease in systemic vascular resistance with an appropriate increase in cardiac output due to afterload reduction, although the increase is not sufficient to prevent a mild decrease in blood pressure. Thus, these data strongly support the underfill theory as the demonstrated sequence of hemodynamic changes occur prior to volume expansion. However, the hemodynamic changes provide potent stimuli for secondary renin release by the kidneys and an activation of the renin-angiotensin-aldosterone system which is typical of those which occur in response to sodium or volume depletion.

The placenta causes arteriovenous shunting of the human maternal circulation up to 20-40 times above the nonpregnant level and accounts for 20% of the maternal cardiac output at term (3). This effect in the latter stages of pregnancy is highly unlikely to be the cause of the early decrease in systemic vascular resistance reported by Phippard. Possible contributors to the early vasodilation are an increased endothelial synthesis of vasodilating prostaglandins, especially E_2 and prostacyclin, which have been demonstrated to occur during human pregnancy (48, 49). Estrogen and progesterone also play some role in systemic vasodilitation (47).

Cardiac

Table 9

Cardiac Changes During Normal Pregnancy

Cardiac output increased 30%-50%
- Increased stroke volume in early and midpregnancy
- Heart rate increased 20%-25% in the last trimester

Decreased systemic vascular resistance
- Begins first trimester, maximal midpregnancy
- Decreased blood pressure begins first trimester, maximal midpregnancy, normal third trimester

Pulmonary artery pressures normal

As in the experimental animals just reported, an increased cardiac output is the most significant cardiac finding in normal women during pregnancy (37-39). The increase begins around the tenth week and reaches a maximum of 30% to 50% above nonpregnant values by the 20th to 24th week. The maximal increase in cardiac output is maintained until shortly before term when it decreases slightly. The increase in cardiac output is almost totally due to an increase in stroke volume during middle pregnancy. The stroke volume then gradually decreases to nonpregnant levels. Heart rate is about 10% higher than normal during middle pregnancy and 20% to 25% above normal in the last trimester.

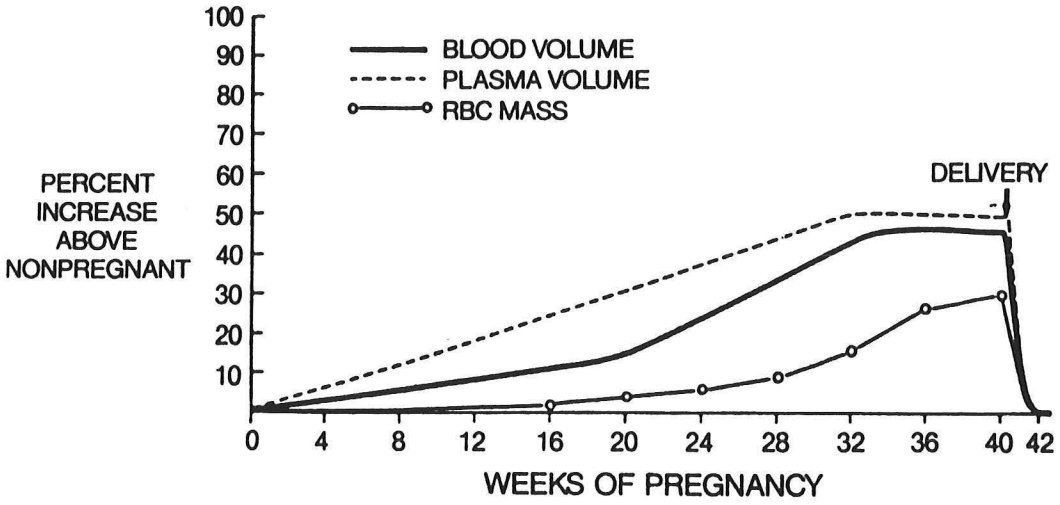
A decreased systemic vascular resistance with secondary decreases in blood pressure begins in the first trimester, reaches its greatest change in midpregnancy and returns to nonpregnant values before term. During midpregnancy pulse pressure widens due to a decrease in diastolic pressure with little change in systolic pressure.

Pulmonary artery pressure is normal throughout pregnancy. Since cardiac output increases without causing a change in pressure, the pulmonary vascular resistance must be less than normal.

Hematologic

Figure 3

Increased Blood Volume During Normal Pregnancy



Scott, A.E.: Obstet Gynecol Annu 1:219, 1972.

The increase in blood volume is predominantly due to an increase in plasma volume during most of pregnancy. The red blood cell mass increases less than the plasma volume and averages about 24% with a range of 12% to 40%. The increasing RBC mass occurs later in pregnancy than the increase in plasma volume. Thus, there is a relative hemodilution that results in the "physiologic anemia of pregnancy". Hematocrits usually range from 33% to 38% with hemoglobin levels of 11 to 12 g/100 ml (38, 39, 45). The increase in red blood cell mass may be caused by a growth hormone-like substance from the placenta (chorionic somatotropin) with additional stimulus by progesterone and perhaps prolactin (38).

SYMPTOMS AND SIGNS SUGGESTING CARDIOPULMONARY DISEASE DURING NORMAL PREGNANCY

Symptoms

Table 10

Cardiopulmonary Symptoms Due to Normal Pregnancy

Symptom	Frequency	Mechanism
Dyspnea	Common	Hyperventilation
Decreased exercise capacity; fatigue	Common	Anemia, increased body weight
Orthopnea, PND	Occasional	Increased intra abdominal pressure
Light headiness syncope	Occasional	Uterine venous occlusion
Chest discomfort	Occasional	Chest wall pain

Zeldis, S.M.: Clinics Chest Med 13:567-585, 1992.

The cardiopulmonary response to normal pregnancy may lead to symptoms and signs suggesting disease. Some of these symptoms have been listed by Zeldis and are recorded in Table 10 (50). Dyspnea is the most common symptom, occurring in up to 76% of women by the 31st week of gestation. Dyspnea usually begins in the first or second trimester and is most prevalent at term (5, 51, 52). Features suggesting physiologic rather than pathologic dyspnea include the onset of the symptom early in pregnancy which does not progress, or even improves as term approaches. Dyspnea due to cardiopulmonary disease is more likely to occur later in pregnancy and become maximal around the seventh month when normal adaptive changes are maximal. Further, physiologic dyspnea is rare at rest, rarely extreme, and the patient typically maintains normal daily activity. Exercise testing usually demonstrates good exercise tolerance (53-55). The exact cause of dyspnea for any reason usually cannot be precisely explained. The same is true in pregnant women, but the consensus is that dyspnea is due to the physiologic hyperventilation leading to a subjective interpretation of shortness of breath.

Decreased exercise capacity and fatigue are thought to be related to the anemia of pregnancy and to the patient's increased body weight (56). Exercise testing reveals no objective

deterioration in exercise capacity during mild to moderate loads (51, 57).

Orthopnea and paroxysmal nocturnal dyspnea occasionally occur in the later stages of pregnancy (39, 56). These symptoms are apparently due to the increased intraabdominal pressure leading to increased respiratory work in the recumbent position (5, 37, 56).

Light headiness or even syncope occasionally occurs in late pregnancy. The cause is compression of the inferior vena cava by the enlarged uterus causing a decrease in venous return to the heart in the supine position (37, 39, 55). This phenomenon may cause as much as a 26% decrease in cardiac output and a 28% decrease in stroke volume compared to sitting or a lateral decubitus position (39, 55, 58). A combination of symptoms including light headiness, syncope, dizziness, weakness, and nausea is referred to as the "supine hypotensive syndrome" and has been reported to occur in up to 11% of normal pregnancies (58).

Chest pain occasionally occurs in the later stages of pregnancy and may be confused with angina. It apparently is due to musculoskeletal pain of the chest wall (59, 60).

Table 11

Misleading Cardiopulmonary Signs Due to Normal Pregnancy

Sign	Frequency	Mechanism
Dependent edema, JVD	Common	Hypervolemia, decreased colloid oncotic pressure, increased femoral venous pressure
Palpable PA, RV Persistently split P_2	Common	Hypervolemia, hyperdynamic right ventrical
Basilar rales, S_3, syst murmur	Occasional Common	Rapid LV filling, increased cardiac output, turbulence
Continuous murmur	Common	Cervical venous hum, mammary souffle

Zeldis, S.M.: Clinics Chest Med 13:567-585, 1992.

Misleading physical signs may also suggest cardiopulmonary disease during normal pregnancy. As previously mentioned, dependent edema is common and is caused by a reduced colloid

oncotic pressure and increased femoral venous pressure. Jugular venous distention is also common and is seen in late pregnancy due to hypervolemia. Taken together, these signs mimic right ventricular failure.

It is also common for normal pregnant women to have a palpable pulmonary artery, hyperdynamic right ventrical, and persistently split second heart sound late in pregnancy (39, 56). These findings, especially when there is jugular venous distention and dependent edema, suggest pulmonary hypertension, but the cause is hypervolemia with a hyperdynamic right ventrical.

Basilar rales due to microatelectasis are occasionally heard (5, 37, 39). Additionally, a third heart sound due to rapid left ventricular filling has been reported in up to 90% of patients in about the 30th week of pregnancy (56). Similarly, an early or mid systolic murmur is heard in up to 96% of patients due to turbulent outflow in the great vessels (61). Taken together, these findings could certainly be mistaken for left ventricular failure.

Two functional, continuous murmurs are common. One is a cervical venous hum that is present in almost all pregnant women. It is best heard over the supraclavicular fossa just lateral to the strap muscles in the neck. It is heard on either or both sides, especially with the patient sitting and looking straight ahead (39). The murmur diminishes if the patient hyperextends her shoulders and brings the elbow well behind the back. A second continuous murmur is a mammary souffle heard late in pregnancy or in the postpartum period. The murmur may be either systolic or continuous but is almost always louder during systole. It is heard in the third or fourth intercostal space and may be bilateral. The murmur is usually best heard in the supine position and may disappear if the stethoscope is pressed firmly against the skin. The murmur is believed to be due to increased flow in the mammary vessels.

THE USE OF DRUGS FOR PULMONARY DISEASES DURING PREGNANCY

Drugs to Avoid in Pregnant Women

Table 12

Abbreviated FDA Pregnancy Risk Classification for Drugs

Category	Controlled Studies in Women	Risk
A.	Yes, negative	Remote
B.	None, but animal studies OK Or animal adverse, women OK	Remote
C.	Animals adverse, none Or no studies in animals or women	Potential benefit> potential risk
D.	Yes, adverse	Potential benefit> Risk if life threatening
X.	Adverse animal and women Or experience with human fetal risk	Contraindicated

When making a decision about the administration of a drug to a pregnant patient, the physician must weigh the risks to the fetus against the benefit to the mother. Once the safety has been assessed, one must be concerned about altered pharmacokinetics in the pregnant woman and monitor closely fetal and maternal effects. Substances ingested by the mother are transported to the fetus beginning about the fifth week of gestation. The transport of compounds across the placenta is determined by the same factors that exist for most membranes, but potentially altered by the change in the environment due to pregnancy. Although there is a concept of protection of the fetus by a placental barrier, most drugs traverse the placenta if present in high enough concentrations for a long enough interval of time (62). Further, since 20% to 40% of umbilical blood flow bypasses the fetal liver directly to the inferior vena cava via the ductus venosus, a substantial portion of any drug crossing the placenta will arrive at the fetal heart and brain undiluted.

When deciding whether to administer a particular drug it would be assumed that data are available concerning the risk to the mother and fetus. Unfortunately, this premise is incorrect, and relatively few data are available. However, the Federal Drug Administration has issued a pregnancy risk classification for drugs, an abbreviated version of which may be found in Table 12.

Drugs may be assigned a category A thru D or X based on the availability or lack of controlled studies in women. Category A drugs have been studied in this manner during the first trimester of pregnancy and have been found to cause no fetal abnormality. Thus, the risk due to the drug is remote. Drugs in Category B have had no controlled studies in pregnant women. However, there are no adverse effects when administered to pregnant animals, or there may be adverse effects in animals, but prolonged usage in pregnant women has not substantiated the animal data. Thus, the risk for use of these drugs is remote. Category C is used for drugs in which there are adverse effects in animals with no controlled studies in women, or there are no studies in animals or women. In fact, the great majority of drugs fall into Category C, because there are no data available. In this circumstance, one must carefully weigh the potential benefit to the mother and compare it to the potential risk to the fetus. The drug should be given only if the potential benefit justifies the potential risk. For example, inhaled beta-agonists such as Metaproterenol and Albuterol are Category C drugs because of a limited experience with their use in pregnancy. If these drugs prevent maternal arterial hypoxemia which may lead to fetal hypoxemia and hypoxia, the potential benefit is well worth the potential risk. In Category D drugs there have been controlled studies in women during the first trimester with the findings of adverse effects to the fetus. In this circumstance the drug should be utilized only if the mother's, and therefore the fetus's, life is threatened. Category X refers to drugs studied in animals and women and shown by each to lead to great risk to the fetus. These drugs are considered to be contraindicated for administration to pregnant women.

Table 13

Physiologic Changes Potentially Affecting Drug Administration in Pregnancy

Decreased gastric emptying 30%-50%.
Decreased gastric and intestinal motility 30%-50%.
Decreased gastric acid 40%.
Increased intra and extravascular volumes.
Tissue volumes of placenta, uterus, fetus.
Decreased albumin concentration, drug binding capacity.
Enhanced liver metabolism.
Increased renal GFR 30%-50% renal plasma flow 25%.

When an appropriate drug for the problem at hand has been determined, one must realize that altered maternal physiology may dictate that the administration may need to be altered from that in nonpregnant patients. Decreased gastric emptying and gastrointestinal motility may lead to erratic absorption. Increased volume of distribution may lead to lower blood levels, while decreased albumin and protein binding may lead to greater

free drug concentrations. Enhanced liver metabolism and GFR may lead to more rapid elimination so that increased loading or more frequent doses may be necessary. If one is not sure of these effects on the drugs being used, a knowledgeable colleague or reference should be consulted.

Table 14

Drugs Used in Pulmonary Disease With Known Adverse Fetal Effects

Drug	Fetal Toxic Effects
Iodine-containing compounds	Hypothyroidism, goiter
Brompheniramine antihistamines	Teratogenic in animals
Coumarin anticoagulants	Nasal cartilage hypoplasia, bone stippling, brachydactyly, intrauterine growth retardation
Antibiotics	
Ciprofloxacin	Fetal arthropathy
Sulfonamides	Hyperbilirubinemia, kernicterus
Tetracycline	Discoloration of teeth, inhibition of bone growth
Chloramphenicol	Gray baby syndrome
Trimethoprim	Possible teratogenic effects
Streptomycin	Eighth nerve damage, deafness
Rifampin	Limb reduction defects

Montella, K.R.: Clinics Chest Med 13:587-595, 1992.

Table 14 reproduces the most recent listing of drugs, December, 1992, used in patients with pulmonary disease which have known adverse fetal effects (63).

Brompheniramine antihistamines were the only agents of this class to show a statistically increased incidence of birth defects in the Collaborative Perinatal Project (64). It's use is not recommended despite the fact that the PDR indicates that it is a category C substance. Coumarin anticoagulants may cause fatal hemorrhage of the fetus in utero in addition to the teratogenic effects indicated in Table 14 and are contraindicated in pregnant women. Ciprofloxacin, the most frequently used agent among the quinolones, has been demonstrated to cause irreversible arthropathy in animals. It is suggested that all the quinolones should be avoided in pregnant women (65).

Sulfonamides are not known to be teratogenic and are classified as Category B in the first and second trimesters.

However, they are rated Category D in the third trimester, because they displace bilirubin from albumin and thereby increase the risk of neonatal kernicterus. Additionally, Sulfonamides may precipitate maternal or neonatal hemolysis in the presence of glucose 6-phosphate dehydrogenase deficiency. Chloramphenicol is a Category C drug but has been associated with the "gray baby syndrome" of cardiovascular collapse in pre-term newborns when administered in the third trimester (66). In addition to the teratogenic changes indicated, tetracyclines subject the mother to potential acute fatty liver and to renal failure. Trimethoprim is listed as a Category C drug, but it is considered contraindicated in the first trimester because it is thought to be teratogenic in animals. Like with other aminoglycosides Streptomycin may lead to ototoxicity (67, 68). Since Streptomycin has been used predominantly in the treatment of tuberculosis and has been largely supplanted by more effective agents, there is little reason to administer this drug. Although Rifampin has been associated with limb reduction defects, central nervous system abnormalities, hypoprothrombinenia, and hemorrhagic disease of the newborn, the incidence of abnormalities has been reported to be low (69). Because Rifampin is a powerful antituberculosis drug, it continues to be recommended as part of the antituberculosis regimen in pregnant women (70).

Satisfactory Drugs in Pregnant Women

Table 15

Antimicrobials Preferred for Use During Pregnancy

Penicillins Pen G, Pen V Ampicillin Amoxicillin Semisynthetic	All are Category B Dosage of Ampicillin, Methicillin increased
Cephalosporins	All Category B except Ceftazidine (unrated) Dosage for all increased
Erythromycin	Category B Do not use estolate due to potential maternal hepatotoxicity

McCormack, et al: Antimicrob Agents Chemother 12:630-635, 1977.

Despite placental transfer which exposes the fetus to 50%-100% of maternal blood concentration, all of the penicillins are ranked as Category B drugs and are considered to be safe for use in pregnant women. Because of the physiological changes indicated previously, blood concentrations of Ampicillin and Methicillin are usually suboptimal when pregnant women are given proper doses for nonpregnant patients. The dose of these two penicillins should be arbitrarily increased from the outset. Since the effects of pregnancy on the absorption, distribution, and elimination of pharmacologic agents not only varies from patient to patient but may also vary within a single patient from time to time, it is extremely important to follow the blood concentrations of all antimicrobials used during pregnancy, and to follow the concentration of other drugs as well if they are available.

Cephalosporins tend to reach fetal concentrations only 20% to 50% of maternal levels protecting the fetus to some extent against their actions. All are Category B except Ceftazidine which is unrated. The beginning dose for all Cephalosporins should be somewhat higher than that for nonpregnant patients.

Erythromycin crosses the placenta to a low degree and is rated a Category B drug. However, the use of Erythromycin estolate is contraindicated due to potentially causing maternal hepatotoxicity (71).

Table 16

Other Antimicrobials Potentially Used During Pregnancy

Aminoglycosides	Category C Decrease dosing interval Potential Ototoxicity
Clindamycin	Category B

McCormack, et al: Antimicrob Agents Chemother 12:630-635, 1977.

As previously indicated all of the aminoglycosides may potentially cause ototoxicity not only in the mother but also in the fetus. Thus these drugs are used only for serious maternal infections and are discontinued as rapidly as feasible. The most experience with use of this class of agents in pregnant women has been with Gentamicin, so it is probably the preferred agent. The dosing interval should probably be decreased with any of the aminoglycosides. Once again, blood concentrations must be followed carefully.

Clindamycin, a drug particularly useful for anaerobic bacterial infections, is rated Category B and should be safe for use during pregnancy.

Table 17

Drugs for Asthma Preferred for Use During Pregnancy

Drug Class	Specific Drug	Dosage
Anti-inflammatory	Cromolyn sodium	2 puffs qid (inhalation) 2 sprays in each nostril bid-qid (intranasal for nasal symptoms)
	Beclomethasone	2-5 puffs bid-qid (inhalation) 2 sprays in each nostril bid (intranasal for allergic rhinitis)
	Prednisone	Burst for active symptoms: 40 mg a day, single or divided dose for 1 week, then taper for 1 week. If prolonged course is required, single a.m. dose on alternate days may minimize adverse effects.
Bronchodilator	Inhaled beta-agonist	2 puffs every 4 hours as needed
	Theophylline	Oral: Dose to reach serum concentration level of 8-12 μg/mL

Expert Panel Report: NHLBI Publication 91:3042, 1991.

The anti-inflammatory and bronchodilator drugs used for asthmatic patients which are preferred for use during pregnancy are enumerated in Table 17. Until recently asthma has been viewed as an intermittent, acute illness caused by bronchospasm, and the major thrust of therapy has been the use of bronchodilators. More recently asthma has been recognized as a chronic condition characterized by airway hyperresponsiveness due to chronic airway inflammation with acute exacerbations of exaggerated bronchoconstriction in response to a variety of physical, chemical and pharmacologic agents. Therapy now focuses on controlling the chronic inflammation which is the major reason for airway hyperresponsiveness. Additionally, emphasis has been

placed on the use of inhaled anti-inflammatory as well as inhaled bronchodilator medicine. The same premises used for the treatment of any asthmatic patient are used for the pregnant asthmatic. Inhaled anti-inflammatory medicines are the first line of treatment, and bronchodilators are utilized only when these fail.

Cromolyn sodium is a nonsteroidal anti-inflammatory agent with little likelihood of fetal harm (72, 73). Its efficacy is less predictable than that of inhaled steroids. A 4 to 6 week trial may be necessary to determine benefit.

Inhaled corticosteroids are currently the major therapy for asthmatic patients. There are three such preparations available commercially. Triamcinolone acetonide is more likely to induce birth defects in animals and the other agents and is listed as a Category D agent (74-76). The use of Flunisolide during pregnancy has not been reported. The largest human experience is with Beclomethasone which has had no adverse fetal effects in humans, and hence it is listed as a Category C drug (77, 78). Thus, Beclomethasone is the inhaled steroid of choice. The agent may require 2 to 4 weeks to exert its maximal effect. The tendency in the recent asthma literature is to continue to increase the dose of inhaled steroids above previously acceptable maximal doses if recurrent asthma is not suppressed.

Since inhaled steroids are not as powerful as systemic steroids, and since inhaled steroids are not useful in treatment of an acute asthmatic attack, it may be necessary to proceed to orally administered drug.

If it is necessary to use oral steroids, short bursts of administration with a rapid taper are preferred. However, if this is not sufficient to control chronic symptoms, a prolonged course may be required. A single morning dose on alternate days may minimize adverse effects, but alternate day steroids may not suffice in some patients. Chronic administration has been associated with decreased birth weight in human offspring (79-81). However, since the fetus is very sensitive to changes in maternal PaO_2, the use of steroids is thought to be safer for the infant than the maternal hypoxemia that may accompany serious disease.

It is recommended that inhaled beta-agonists are used only on an as needed rather than a constant dose regiment. Inhaled terbutaline is a Category B agent, while Metaproteronal and Albuterol are Category C drugs. In a recent controlled trial, no adverse fetal effects were found from the use of inhaled agents (82).

There are no advantages to administering beta-agonists orally or subcutaneously rather than by inhalation. Further, there have been serious side effects when beta 2 agonists have been administered subcutaneously as a tocolytic agent to suppress

uterine contractions in premature labor (83, 84). These side effects include water retention and pulmonary edema which is apparently due to volume overload. Although patients tend to respond rapidly to therapy with diuresis and oxygen administration, several deaths have been reported.

Although Theophylline is not a powerful bronchodilator, it is usually added to a regimen which does not control symptoms of asthma with inhaled steroids and inhaled beta 2 agonists. Theophylline has been used extensively in pregnant asthmatic patients without reported fetal or maternal side effects and is hence labelled a Category C drug. There is apparently a reduction of Theophylline clearance of 20% to 35% in the third trimester. Since fetal Theophylline levels are similar to those of the mother, blood concentrations should be checked frequently, especially in the third trimester. It is thought that the blood concentration should not exceed 8-12 μg/ml.

Table 18

Drugs for Asthma and Associated Conditions
Preferred for Use During Pregnancy

Drug Class	Specific Drug	Dosage
Antihistamine	Chlorpheniramine	4 mg by mouth up to qid 8-12 mg sustained-release bid
	Tripelennamine	25-50 mg by mouth up to qid 100 mg sustained-released bid
Decongestant	Pseudoephedrine	60 mg by mouth up to qid 120 mg sustained-released bid
	Oxymetazoline	Intranasal spray or drops up to 5 days for rhinosinusitis
Cough	Guaifenesin Dextromethorphan	2 tsp by mouth qid
Antibiotics	Amoxicillin	3 weeks therapy for sinusitis

Expert Panel Report: NHLBI Publication 91:3042, 1991.

The agents listed in Table 18 are those recommended by the Asthma Education Program for symptom relief in pregnant women.

Next, I shall briefly review deep venous thrombosis and pulmonary embolism because of the frequency and serious consequences of these problems.

DEEP VENOUS THROMBOSIS (DVT) AND PULMONARY EMBOLISM (PE)

Incidence

Table 19

Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE) in Pregnant Women

Frequency approximately 1/2500 deliveries
Five times more common in pregnant than in nonpregnant women
Occurrence by trimester 24%/44%/31%
More frequent postpartum than during pregnancy?
Second leading cause of death of pregnant women

The reported frequency of DVT/PE among pregnant women has varied significantly (85, 86). However, the fact that investigators at Brigham and Women's Hospital and Parkland Hospital agree that a DVT/PE occurs approximately once in every 2,500 deliveries makes this a reasonable estimate, since each have studied very large patient populations (87, 88). Although the mechanisms have not been worked out, it is highly probable that pregnant women are hypercoagulable (89-95). Perhaps of even more importance, there is a marked tendency to venous stasis. Thus, a Consensus Conference sponsored by the National Institute of Health has estimated that the frequency of DVT/PE is five times more common in pregnant that in nonpregnant women (96). Although one might anticipate that thrombosis would occur more frequently in the last trimester, the actual occurrence is approximately that indicated in Table 19 (86, 97). It has generally been accepted that there are more DVT/PE postpartum than during pregnancy. However, the data from Parkland for the three years ending in 1992 are that 20 of 24 cases of DVT/PE were identified antepartum (98). Irrespective of when DVT/PE occur in relationship to pregnancy, it was second only to trauma as the leading cause of maternal death in Massachusetts from 1982 through 1985 (99).

Diagnosis

Table 20

Signs and Symptoms in 327 Patients
with Proven Pulmonary Emboli

Deep Venous Thrombosis	Pulmonary Emboli		
Pain or Tenderness	Chest Pain	88%	
Edema	Pleuritic		74%
Redness	Non pleuritic		14%
Warmth	Dyspnea	84%	
	Cough	53%	
	Hemoptysis	30%	
	Respirations >16	92%	
	Pulse >100	44%	

UPET: Circulation 47(Supplement II):II 81-II 85, 1973.

The diagnosis of deep venous thrombosis is usually suggested by pain or tenderness in the patient's lower extremities, edema of one or both legs, redness and warmth. However, many studies have shown that depending on clinical signs and symptoms for a diagnosis is literally no better than the toss of a coin (100-103). Moreover, as indicated in the Urokinase Study Trial of 327 patients with proven pulmonary emboli, the clinical signs and symptoms of PE are also non specific (104). Considering the potential detrimental effects of unnecessary treatment with anticoagulants or of lack of treatment of a patient with DVT/PE, some objective test to establish a diagnosis more firmly is indicated whenever DVT/PE has been suggested by clinical signs and symptoms.

Contrast venography has historically been considered to be the "gold standard" for the diagnosis of DVT. A recent editorial by Dr. Helen Redman of our institution suggests that more recently standardized noninvasive testing is at least as satisfactory (105). The present technique utilizes a combination of B-mode ultrasonography with a pulsed or color Doppler (duplex scanning). In the hands of an experienced operator, studies comparing ultrasonography with contrast venography have indicated a 95% sensitivity and a 98% specificity in over 1,500 patients (106-125). The technique is poor for detecting thrombosis limited to calf veins. However, it has been demonstrated that only about 20% of calf vein thromboses extend upward into the popliteal veins and become a threat for pulmonary emboli (126-129). Thus, patients with thrombosis limited to the calf are usually not treated with anticoagulants unless serial testing

demonstrates an extension of the thrombus to the popliteal veins (130).

Table 21

Fetal Radiation Doses with Procedures Used to Diagnose PE

Procedure	Estimated Fetal Exposure (Rads)
Chest x-ray	<0.001
Ventilation ^{133}Xe lung scan	0.004 - 0.019
Perfusion ^{99m}Tc-MAA scan (1-2 mCi)	0.006 - 0.012
Pulmonary angiography (Brachial route)	<0.050
Pulmonary angiography (Femoral route)	0.221 - 0.374

Ginsberg, et al: Thromb Haemost 61:189-196, 1989.

Unfortunately, all of the procedures used to make a more definitive diagnosis of PE cause fetal irradiation and lead to concerns about childhood cancer or teratogenesis. For this reason, Ginsberg and his colleagues have recently studied fetal risks associated with levels of radiation (131). A literature review indicated that there is a very small increase in the risk of childhood cancer following low dose (less than 5 rads) in utero radiation exposure. These investigators then calculated levels of radiation exposure to the fetus for the diagnostic procedures which might be used to diagnose pulmonary embolization. These estimates are reported in Table 21. Although one should avoid any exposure if possible, the investigators conclude that "the risk of such exposure is small, both in relative and absolute terms". Virtually all authorities agree that the risks of untreated pulmonary emboli or of unneeded anticoagulant therapy are greater than those of radiation.

Table 22

PIOPED Results Among Patients with Successful Pulmonary Angiograms

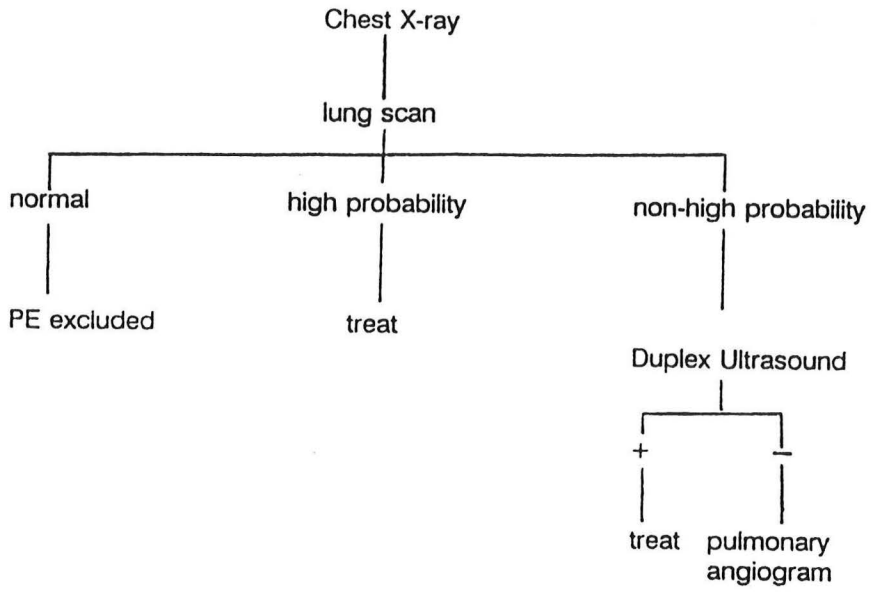
$\dot{V}/\dot{Q}$ Scan Interpretation	PE Present		PE Absent		Pts. Per Group	% Total Pts.
	n	%	n	%		
High	102	88%	14	12%	116	16%
Intermediate	105	33%	217	67%	322	44%
Low	39	16%	199	84%	238	33%
Normal	5	9%	50	91%	55	8%
Total	251	34%	480	66%	731	100%

PIOPED: JAMA 263:2753-2759, 1990.

The recent study of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) used pulmonary angiograms as the "gold standard" for the diagnosis of pulmonary embolism to determine the usefulness of ventilation/perfusion scanning. Among the 731 patients studied 251 or approximately one-third were found to have pulmonary emboli. If the scan was interpreted as a high probability of pulmonary emboli 88% of the patients were correctly diagnosed. However, a substantial number of patients with emboli had an intermediate scan, and a not insignificant number had a low probability designation. Combining clinical assessments with the V/Q scan interpretation improved the probability of making the correct diagnosis. Thus, among patients in whom the clinical impression and the scan interpretation were both of high probability, 96% had pulmonary embolism. A low probability of clinical assessment when paired with a low probability V/Q scan correctly excluded the diagnosis in 96% of patients. A normal V/Q scan when compared with a low likelihood clinical assessment correctly excludes pulmonary embolism in 98% of patients. These findings have been interpreted to mean that a high probability scan is sufficient for making a diagnosis of pulmonary emboli, and a normal scan is sufficient for ruling out pulmonary emboli. Intermediate and low probability scans are not satisfactory for making a correct diagnosis. Unfortunately, only 16% of patients have high probability scans and 8% normal scans. Thus, scanning is not definitive in 75% to 80% of patients and additional testing is necessary. In many Centers if the scan is neither normal nor high probability the physician proceeds directly to pulmonary angiography. Demers and Ginsberg, however, suggest a different algorithm which may decrease the number of pulmonary angiograms when scanning is not definitive (132).

Figure 8

Suggested Order of Diagnostic Tests for the Diagnosis of Pulmonary Embolism



Demers, et al: Clinics Chest Med 13:645, 1992.

Although it is rarely diagnostic of pulmonary embolism a chest x-ray is obtained in all patients to help interpret the scan results and to determine if some entity which might mimic the clinical findings of a pulmonary embolus, such as a pneumothorax, exists. In the great majority of patients it has been necessary to proceed to a lung scan. If the scan is normal a pulmonary embolus has been virtually excluded. If the scan is interpreted as high probability sufficient evidence exists to diagnose a pulmonary embolus, and one proceeds with anticoagulant therapy. In the event of a scan interpretation of indeterminate or non-high probability the lower extremities are studied by duplex ultrasound. If DVT is diagnosed there is sufficient evidence to proceed with anticoagulant therapy. However, if the ultrasound is negative, a pulmonary angiogram is obtained. More recently Stein, Hull and collaborators have reanalyzed the combined data from PIOPED and from the Canadian Study Group (132a). Their suggested algorithms rely as heavily on the clinician's assessment of probability of DVT/PE as on the V/Q scan and duplex scanning and are even less aggressive in proceeding to a pulmonary angiogram.

Therapy

Table 23

Anticoagulant Therapy for DVT/PE During Pregnancy

Adverse outcomes during anticoagulant therapy were 148/567 (26.1%) with warfarin and 10/278 (3.6%) with heparin.

Heparin therapy is initiated intravenously with a 5000 unit bolus followed by a continuous infusion of 24,000 to 32,000 units/24h to prolong the aPTT to 1.5 to 2.5 times control.

After 4-5 days administer subcutaneous heparin every 12 h to maintain aPTT 1.5-2.5 times control at 6h postinjection throughout pregnancy.

Ginsberg, et al: Thromb Haemost 61:197-203, 1989; Ginsberg, et al: Arch Intern Med 149:2233,2236, 1989.

As indicated previously warfarin may be teratogenic when administered during weeks 6-12 of pregnancy. Additionally, Ginsberg and his colleagues have reported that central nervous system abnormalities may be associated with warfarin at any time during pregnancy (133, 134). Thus, heparin is the therapy choice for DVT/PE during pregnancy. A reasonable regimen is indicated in this table. For women who object to subcutaneous injections twice daily for a protracted interval, a Teflon catheter that is replaced on a weekly basis may be utilized (135). Heparin is discontinued at the onset of labor and restarted as soon as hemostasis is obtained. Warfarin therapy is started the same day, and the heparin is discontinued when the level of warfarin has become therapeutic. Oral anticoagulants are usually continued for an additional three months postpartum.

I am not aware of any specific outcome data for pregnant women. For the 375 patients in the PIOPED study who were followed for one year, only 10 (2.5%) died of pulmonary embolism (136). Eight of these deaths occurred in one week and 9 within 2 weeks of entry into the study.

CRITICAL CARE

Table 24

Obstetric Patients Requiring Critical Care

1. OB ICU's in proximity to L and D usually care for antepartum OB complications, especially pregnancy-induced hypertension and hemorrhage.

2. MICU's remote from L and D more commonly care for postpartum patients with medical diseases, especially respiratory failure and infections.

3. MICU patients should be cared for by both ICU and obstetrical teams, especially if the patient is pre-term. Fetal survival has been reported to be 75% for MICU deliveries.

4. Although the total number of pregnant women requiring MICU care is small, a high fraction of these have ARDS. Almost all mortality is from the ARDS patients.

5. ARDS is almost always associated with infection.

Finally, some mention should be made concerning obstetrical patients requiring critical care (137-143). Although some obstetrical intensive care units care for medical problems which happen to arise during pregnancy, most OB ICU's are in proximity to a Labor and Delivery suite and care predominantly for antepartum OB complications, especially pregnancy induced hypertension and hemorrhage. This tendency is influenced, in part, by the very low incidence of pregnant women with serious medical diseases which make it difficult for obstetricians to obtain and maintain skills necessary for the care of critically ill patients. Thus, this type of patient, especially those with ventilatory failure, are usually transferred to a Medical Intensive Care Unit; the tendency for transfer is greater in postpartum rather than antepartum patients. If such an arrangement exists, patients should be cared for conjointly by ICU and obstetrical teams of physicians. Close cooperation is especially necessary if the patient is prenatal. When it exists fetal survival has been reported to be about 75% for MICU deliveries.

Although the total number of pregnant women requiring MICU care is small, a high fraction have the Adult Respiratory Distress Syndrome. Indeed, almost all mortality of obstetrical patients in MICUs is ARDS. Interestingly, the etiology of ARDS in pregnant or postpartum patients is almost always infectious.

SUMMARY

Despite an increase in intraabdominal pressure and cephlad displacement of the diaphragms, pulmonary function tests are normal in pregnant women. There is marked hyperventilation throughout pregnancy due to high blood concentrations of progesterone. There is a tendency, worse while recumbent, to a moderate mismatching of ventilation and perfusion resulting in an increased A-a gradient and low PaO_2.

Cardiovascular response is dominated by a marked increase in plasma volume due to decreased systemic vascular resistance with stimulation of the renin-angiotensin-aldosterone system. In early pregnancy the cardiac output is high due to an increase in stroke volume.

The increased cardiac output is maintained in late pregnancy by an increased heart rate rather than an increased stroke volume. The increase in plasma volume is not matched by a sufficient increase in RBC mass leading to the "physiologic" anemia of pregnancy.

The normal cardiopulmonary changes may lead to signs and symptoms of disease.

Some drugs may lead to adverse fetal or maternal effects and should be avoided in pregnant women. Drugs and antimicrobials of FDA categories A, B, C are generally safe, while categories D, X, and unrated should be avoided if possible.

Pulmonary emboli are more frequent in pregnant than non-pregnant women. Diagnosis can usually be made with a combination of clinical judgement, V/Q scanning and duplex ultrasound testing for DVT. Coumadin should be avoided and the patient treated with heparin until after delivery.

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