

Mini-Review

Nine things internists and family practitioners need to know about pregnancy

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Background: Pregnancy is a transient biologic event that has long-term implications for maternal health. The clinicians must understand the normal physiologic alterations of pregnancy to provide preconception counseling and appropriate medical management during and after pregnancy.

Objective: This review focuses on ten important normal gestational events that all primary care physicians need to keep in mind when caring for pregnant patients.

Keywords: Maternal health, medical management, pregnancy, primary care, women.

Pregnancy is a remarkable, transient biologic event that has long-term implications for maternal health and has implications for women with underlying medical conditions becoming pregnant. Understanding the normal physiologic alterations of pregnancy allows the clinician to provide preconception counseling and appropriate medical management during and after pregnancy.

This short review focuses on nine important normal gestational events that all primary care physicians need to keep in mind when caring for pregnant patients (**Table 1**).

1) Immunologic state

The first series of events is what I call the “immune ballet” of gestation, an immunologic relationship between the mother and the fetus necessary for successful implantation and progression of the pregnancy to a 40 to 42 week conclusion. Fertilization of the egg usually takes place in the fallopian tube. The mother must recognize that she has conceived and that her endometrial tissue needs to be prepared to accept the arriving conceptus so that placental implantation can begin and proceed to the fully formed hemochorial organ. Because the conceptus has 50 percent of its DNA from paternal sources, there may be substantial histocompatible differences that need to be accommodated so that

placental implantation can occur. The mother’s lymphocyte mediated immunity is very subtly altered during the first 12 to 16 weeks of gestation; alterations that may foster changes in olfactory and gustatory sensation and nausea and vomiting.

Pregnant women are not immunodeficient, but they are “immunodifferent” during the course of gestation. B-cell function and production of antibodies is unchanged. Existing humoral immunity does not change during gestation. Pregnant women can be immunized successfully; nonliving antigens can be used safely in pregnancy. The use of influenza vaccine, diphtheria tetanus toxoid, hepatitis A and B and rabies vaccines are all safe and recommended to be administered in susceptible pregnant women. Live virus and bacterial vaccines are not used in pregnancy except under certain circumstances because of the risk of unusual responses to live vaccines and the potential for transplacental passage of the vaccine virus. Pregnant patients may have alterations in the susceptibility to and a more aggressive course of infections by pathogens that are contained or eliminated by cell mediated immunity (**Table 2**). The clinical course of certain fungal, mycobacterial, and viral infections may be different during pregnancy. For example, primary influenza pneumonia during pandemic and epidemic influenza episodes is increased in pregnant women, especially women in the second and third trimester of pregnancy. Similarly, chickenpox in susceptible pregnant women may have a more aggressive course with an increased risk for serious and sometimes fatal Varicella pneumonia. Malaria is well known greater threat during pregnancy.

Table 1. Important normal gestational events that affect the clinical course and management of medical conditions.

1.	Immunologic recognition of conception and accommodation of placentation
a)	Changes in T cell function
b)	Changes in response to intracellular pathogens
2.	Increased ventilation
a)	Decreased arterial PCO ₂
b)	Hyperventilation symptoms
3.	Increased coagulation factors
4.	Increased blood volume
a)	Increased glomerular filtration
b)	Increased total body water
c)	Decreased concentration of endogenous and exogenous substances
5.	Increased cardiac output
6.	Decreased serum albumin
7.	Tubal relaxation
8.	Mechanical effects of the gravid uterus
9.	Metabolic effects of the placenta
1)	Increased insulin resistance

Table 2. Some infectious diseases with changes in clinical course because of pregnancy.

Syphilis	} Transplacental infection
Listeria	
HIV	
Leprosy:	Movement of clinical lesions from tuberculoid to lepromatous histology
Influenza	} Primary viral pneumonia
Varicella	
Malaria:	Placental sequestration of <i>P. falciparum</i>

2) Respiratory function

Increases in progestational hormones stimulate the central ventilatory drive in pregnancy. Early in pregnancy patients will have a decline in their resting arterial PCO₂. The normal arterial PCO₂ in pregnancy is 30 to 32 torr, not 40 torr. Pregnant patients have hyperventilation symptoms frequently; symptoms that may be confused with cardiovascular or underlying chronic pulmonary disease (**Table 3**). The biggest

risk is for misinterpretation and mismanagement of arterial blood gases in patients with asthma or pulmonary infections. Since the normal arterial PCO₂ in pregnancy is 30 to 32, clinicians in the emergency room and hospital need to be aware that a pregnant asthmatic patient with an arterial PCO₂ of 38 torr is hypoventilating and needs vigorous management including hospitalization.

Table 3. Hyperventilation syndrome.

Symptoms	Signs
1. Apprehension and anxiety	
2. Dyspnea "Can't get enough air in"	Tachypnea Hyperpnea
3. Palpitations	Tachycardia Premature atrial beats Ectopic unifocal ventricular beats
4. Chest pressure/pain	
5. Paresthesia	Acral and circumoral paresthesias Tetany (carpopedal spasm)
6. Faintness, lightheadedness	Syncope

3) Increased clotting factors

Pregnancy is accompanied by increases in virtually all clotting factors, changes that also begin early in gestation. Pregnancy is normally associated with diminution in some thromboprotective substances such as protein S and antithrombin III. Pregnancy by itself is a thrombophilic risk but pregnancy can be a magnifying event for women with preexisting thrombophilic conditions. Thromboembolic events occur throughout pregnancy not just in the third trimester or the intra and postpartum periods (**Fig. 1**). Clinical evaluations of pregnant patients with dyspnea, hyperventilation symptoms, and chest discomfort should be carefully evaluated for the possibility of thromboembolic events, especially pulmonary emboli. Because of the normal decline in arterial PCO₂ arterial blood gases may not be a reliable indicator of pulmonary embolization.

4) Increased blood volume and cardiac output (Table 4)

Gestation is accompanied by retention of salt and water as well as increases in red cell mass. By the 16th to the 18th week of gestation a pregnant patient may have a 50 percent increase in circulating blood volume. Since plasma formation is greater than red cell mass expansion there is a "physiologic anemia of pregnancy." There is an increase in total body water which may lead to changes in drug distribution. The patient's cardiac output increases with increases in stroke volume and in pulse rate. In association with the propensity to hyperventilation symptoms, patients may complain about palpitations and breathlessness which sets the stage for further cardiovascular evaluation. Because of the increased blood volume and increased cardiac output women with obstructing cardiovascular lesions such as aortic stenosis,

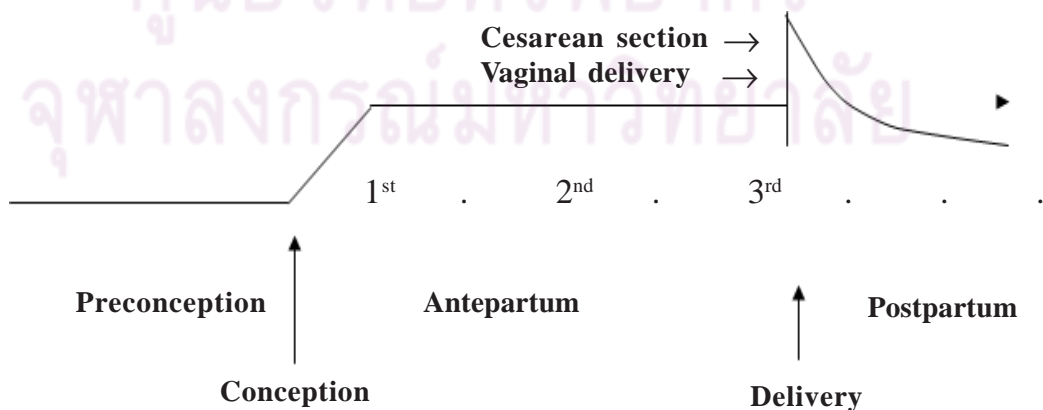


Fig. 1 When do thromboembolic events occur?

Table 4. Effects of increased blood volume.

a. Increased cardiac output
b. Increased glomerular filtration Decreased concentrations of BUN, creatinine, uric acid
c. Increased total body water Changes in drug distribution and concentration
d. Increased risk for cardiorespiratory problems in patients with stenotic cardiovascular lesions

coarctation of the aorta, and mitral valve stenosis have greater risks for cardiorespiratory symptoms and decompensation. In the past silent mitral stenosis was often a diagnosis established during pregnancy when increased blood volume resulted in increased left atrial volume and pressures with pulmonary venous engorgement, decreased pulmonary compliance, and symptoms of dyspnea on exertion and occasional seemingly spontaneous acute pulmonary edema.

A major consequence of increased blood volume and increased blood flow to the uteroplacental unit and kidneys are increased glomerular filtration and excretion of endogenous substances and drugs by the renal route. The normal glomerular filtration rate after the 14th to 16th week of gestation is 130 to 150 ml/min, not 100 ml/min. The result is that serum levels of BUN, creatinine, and uric acid decline during pregnancy. The normal levels for pregnancy should be at the lower limit of nonpregnant values.

5) Decreased serum albumin

As blood volume and body water expand, there is a decline in the normal serum albumin and other plasma proteins so that the normal serum albumin during the second and third trimesters is 3 gm/l, not 4 gm/l. The total serum calcium may decline to lower limits of normal without the patient noting signs of hypocalcemia and tetany because the ionized calcium remains in normal range.

Pregnant patients have a decrease in colloid osmotic pressure which means that they tend to form edema easily. Dependent edema of the lower legs is common and can be exacerbated by prolonged sitting. The decline in serum colloid osmotic pressure also fosters the formation of pulmonary edema particularly in patients with obstructive mitral valve disease or in patients that are over hydrated. A not uncommon

clinical event is an otherwise healthy woman with a normal pregnancy who has prolonged labor for which she receives an epidural anesthetic. When the blood pressure declines, as expected with relaxation of lower limb vasculature, the patient is given additional crystalloid fluids. If labor and delivery are protracted the patient may receive as much as two or three liters of crystalloid fluid. On return to the floor following delivery the epidural anesthetic wears off with return of vasoreactivity and an influx of the additional crystalloid sequestered in the lower limbs into the circulation. With a serum albumin of < 3.0 gm/l the patient may develop cough and dyspnea with basilar rales consistent with pulmonary edema, a condition easily treated with small doses of diuretic.

6) Tubal Relaxation (Table 5, 6)

Gestation produces increased blood volume and decreases in peripheral vascular resistance. As the patient's blood volume is expanding, there is relaxation of all muscular tubes with a decline in blood pressure. Patients with preexisting hypertension on medication may develop orthostatic symptoms requiring changes in their antihypertensive regimen. As normal pregnancy progresses past the 26th to 30th week the blood pressure gradually returns to pre-pregnancy levels. Toxemia of pregnancy, now called preeclampsia, is a unique condition complicating human gestation. Preeclamptic patients often do not have the decline in peripheral vascular resistance or maintain nonpregnant peripheral vascular resistance so that their blood pressure rises.

The gastrointestinal tract has decreased force and frequency of peristalsis so that pregnant patients are at risk for constipation and for gastroesophageal reflux and aspiration pneumonitis. Lower esophageal pressures decline and gastric emptying is reduced as

Table 5. Tubal relaxation normal for pregnancy.

- Decreased peripheral vascular resistance: ↓ blood pressure
- Decreased venous tone: ↑ venous varicosities
- Decreased gastrointestinal tract tone and peristaltic force:
 - ↓ lower esophageal sphincter tone
 - ↓ gastric emptying
 - dilatation of gallbladder
 - ↓ colonic motility
- Decreased ureteral tone and peristaltic force

} Gastroesophageal reflux

Table 6. “Normal” consequences of tubal relaxation.

- Alterations in cardiovascular hemodynamics
- Propensity to form or exacerbate varicose veins and dependent edema
- Gastroesophageal reflux
- Formation of biliary sludge and gallstones
- Constipation
- Increased frequency of urinary tract infection: pyelonephritis
- Painful distension of renal pelvis

a result of pregnancy related tubal relaxation which means that gastroesophageal reflux is common with heartburn and episodes of nocturnal aspiration. The new onset of wheezing and cough in a pregnant patient should alert the clinician to the very real possibility that the patient has significant gastroesophageal reflux and nocturnal aspiration. Not only are muscular tubes affected, so is the pelvic girdle. The placental hormone, relaxin, tends to cause loosening of the pubic symphysis and the sacroiliac joints so that instability of the pelvis becomes a potential and may be accompanied by disabling pelvic girdle and back pain.

The urinary collecting system dilates and has reduced peristaltic force and frequency enhancing the risk for ascending urinary tract infection. Acute pyelonephritis can have adverse impact on pregnancy outcome and requires vigorous, microbiologically appropriate, antibiotic treatment.

7) Mechanical effects of the gravid uterus (Fig. 2)

The gravid uterus expands out of the bony pelvis

at around the 18th to the 20th week of gestation. Late in pregnancy, when the patient is supine, the gravid uterus can compress the inferior vena cava with substantial reductions in venous return which exacerbate lower leg edema and varicose veins and reduce cardiac output. Uterine compression of already dilated ureters fosters the development of renal pelvic distension and urinary tract infections. Seriously ill pregnant patients, particularly those with cardiovascular conditions or urinary tract infections, need to be positioned carefully so that the gravid uterus does not complicate their cardiac function or clearance of infection from the upper urinary tract. An additional complication of the gravid uterus is that as it continues to expand into the abdominal cavity, it may produce stretching of the abdominal musculature with the resulting nerve entrapment syndrome almost always in the subcostal region and associated with boring, continuous dysaesthesia type pain with changes in light touch and pinprick sensation in the affected area.



Fig. 2 Gravid uterus.

8) Metabolic effects of the placenta

The placenta is a true metabolic factory! Perhaps the most important endocrinologic effect of a healthy placenta is increased insulin resistance leading to alterations in glucose metabolism. In a normal pregnancy, especially after the first trimester, a woman may need to produce and release three to five times as much insulin in order to maintain euglycemia. There is no question that euglycemia is the appropriate state for pregnancy and that gestational changes in glucose levels need to be managed with dietary instruction and changes in insulin dosing in patients that require insulin or that have preexisting diabetes. It is important to recognize that the placenta continues to grow and to produce its metabolic effects until the 36th to 38th week of gestation so that frequent monitoring of blood glucose and alterations in diet and insulin management are essential. One of the features of contemporary obstetric medicine is the increasing numbers of obese women entering pregnancy with increased insulin resistance and developing gestational diabetes.

Polycystic ovarian syndrome with obesity, infertility, and insulin resistance responds metabolically to Metformin which reduces hyperinsulinemia and restores fertility. Patients that conceive on Metformin need to be treated as gestational diabetics with dietary adjustments and regular home glucose monitoring. Whether Metformin should be continued during pregnancy is debated, but insulin should be used to manage hyperglycemia when present.

9) Preconception counseling

Because of the remarkable physiologic changes of normal pregnancy, it is essential for primary care clinicians to talk about sex and pregnancy with their patients. Effective management of existing medical conditions such as hypertension, diabetes, and seizure disorders need to be discussed. Better education of patients about the physiologic events of gestation is essential including discussions about medications. Considerable anxiety surrounds the administration of drugs during pregnancy. The FDA classification for drugs currently in use is oriented primarily to teratogenesis (**Table 7**) and may not adequately

Table 7. Pregnancy risk classification by food and drug administration (FDA), USA.

A: Controlled human studies fail to demonstrate risk
B: Safe in animals (no human data), or adverse effects in animals; human studies (no effect)
C: Adverse effects in animals but no human data, or no animal or human studies available
D: Evidence of risk but benefits may outweigh risk
X: Contraindicated in virtually all circumstances

reflect clinical benefit or necessity for the pregnant patient. Some medications need to be discontinued, such as retinoids and certain oral hypoglycemic agents. Some medication regimens should be simplified; for example, patients on multiple drugs for seizure control. Angiotensin converting enzyme blockers and receptor blockers should be discontinued by the end of the first trimester but many doctors prefer to find alternative antihypertensive drugs before conception. Other medications like insulin and antihypertensives will need dosage adjustments according to the course of gestation. Many medications should be continued and not discontinued because they are essential for stable maternal health.

Changes in the population of women becoming pregnant have emphasized the importance of an understanding of gestational physiology and the interaction of pregnancy and medical conditions. The number of pregnancies among women over 35 years of age has increased because of career choices and the availability of assisted reproductive technology. The number of women with serious, chronic medical

conditions, such as cystic fibrosis, type I diabetes, and a variety of organ transplants, living well enough to be able to conceive and sustain successful pregnancies has dramatically increased. All of these patients require careful preconception counseling and a functioning obstetrical and medical team for pregnancy and post pregnancy care.

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