Chapter 2
Normal Pregnancy, Pregnancy Complications, and Obstetric Management

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Introduction

Profound changes in maternal physiology occur during pregnancy to accommodate the growing fetus. Understanding these changes is fundamental to proper management of the obstetric patient and identification of pathologic changes. This is of great importance as reproductive-aged women are disproportionately affected by rheumatic diseases, and in some cases an initial diagnosis is made in the course of an evaluation for adverse obstetric outcomes. In this chapter we first address normal fetal development followed by the various physiologic changes that occur in major organ systems. Next we address antenatal care and fetal surveillance. Finally we discuss common complications of pregnancy. As some of these complications occur with greater frequency in the obstetric patient with underlying rheumatic disease or may be confused with relapse or exacerbation of rheumatic disease(s), understanding the nuances in management will serve as a basis for understanding modifications that may be required in the management of the woman with underlying rheumatic disease.

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Embryonic Development and Fetal Physiology

The ovum is fertilized in the Fallopian tube and makes its way to the uterus over the course of 5–6 days. During this time, the rapidly dividing cells of the fertilized ovum undergo blastulation, a process by which the cells of the zygote take the shape of a fluid-filled structure with distinct external and internal cellular components. The resulting blastocyst is composed of external cells destined to interact with the uterine endometrium and form the placenta, while a separate group of cells form the inner cell mass, destined to form the embryo and enclosing membrane structure.

The blastocyst reaches the uterine cavity about 1 week after fertilization and implants in the endometrial lining (endometrium) of the uterus on average 9 days after fertilization, though it may occur as early as 6 days and as late as 12 days. Human chorionic gonadotropin (hCG), produced by trophoblast (placenta) tissue, is secreted at the blastocyst stage and is first detectable in the urine and blood of pregnant women 8–10 days after conception (day 22–24 of a 28-day menstrual cycle).

The most external of the trophoblastic cells of the blastocyst in contact with the endometrium form an invasive, mutlinucleated syncytium, the *syncytio*trophoblast. The syncytiotrophoblast is to be distinguished from more proximal, single-cell *cyto*trophoblast. After implantation, the synctyiotrophoblast just under the forming embryo and amniotic cavity thickens and then forms vacuolar spaces. The resulting matrix of cellular trabeculae and vacuolar spaces are the precursors of the placental villi and intervillus spaces. In the third week after conception, the fetal villus vasculature begins to form.

For most of the first 10 weeks of pregnancy, the lacunae of the forming placenta are filled with clear fluid, without the presence of a genuine relationship between maternal and embryonic circulations. During this period gas and nutrient exchange with the embryonic structures is of a passive nature, with intervillus space oxygen concentrations being <20 mm Hg. In the meantime, the terminal portions of the uterine arteries that penetrate into the decidualized endometrium, known as spiral arterioles, have undergone remarkable transformation, with replacement of vascular wall smooth muscle and elastic fibers with fibrinoid. The initial result is a dilated and nonmuscular terminal arteriolar structure.

Within the first few weeks of pregnancy, cytotrophoblastic cells that have migrated peripherally, known as extravillius cytotrophoblasts, associate with the altered terminal spiral arterioles. Other important changes in the maternal vasculature have been in play. The more distal segments of the spiral arteries also dilate under the influence of pregnancy-related hormones, and the overall maternal blood flow to the uterus begins to increase considerably.

Around 10–12 weeks gestation the cellular occlusion of terminal spiral arterioles begins to clear, allowing maternal blood to enter the intervillus space and bathe the fetal villi. With this the oxygen tension in the intervillus space rises. Concomitant maturation of the fetal villi and fetal production of capable (non-nucleated) erythrocytes complete the requirements for a true placental circulation. The key

components of this circulation are that it is of relatively high volume and low velocity such that the pressure within the intervillus space is also relatively low, lower than that in the fetal villous vasculature. The net result is that oxygenated maternal blood can enter the intervillus space and bathe the delicate fetal villi without damaging or collapsing them.

At the time of implantation, the blastocyst contains about 200 cells. The inner cell mass, or embryonic disc, is distinguishable from the trophoblastic cells of the blastocyst. Within a few days, the embryonic disc forms into two cell layers, the primitive ectoderm and the underlying endoderm. The "embryonic period" of development begins at the beginning of the third week after fertilization, or the fourth menstrual week. In the ensuing 8 weeks, all major organs of the embryo are formed, though further development of organs occurs in the subsequent fetal period (tenth menstrual week).

The events that take the embryonic disc to that of a fully formed embryo with all major organs in place are quite obviously complex and occur in a well-delineated sequence. Cardiac formation can serve as an example. In the fifth menstrual week, the appearance of a splanchnic mesodermal layer of cells allows the development of the embryonic vasculature. One element, the primitive heart tube, appears in the fifth menstrual week when two adjacent midline endothelial tubes fuse. Surrounding splanchnopleuric mesoderm condenses to form a mantle of myoepicardium. Subendocardial tissue forms from connective tissue between the endocardium of the primitive heart tube and the myoepicardial mantle. This primitive structure begins to contract in the early fifth menstrual week and is visible pulsatile by high-resolution ultrasound by the end of the fifth menstrual week. The tubular structure bulges in five regions along its length, each destined to form an adult cardiac structure, but with the future atrial and sinus venosus tissues lying caudal to the future tissues that form the ventricles and major artery outflows. The tubular heart structure undergoes rightward looping, pushing the future ventricular and atrial regions into their adult relationships with the atrial tissues lying cranial to the ventricular tissues. Subsequently, complex partitioning of the tissues occurs in sequence resulting in a 4-chambered heart by the eighth menstrual week. Recognizable neonatal cardiac defects may result when this process goes awry. Failure of the formation of a septum between the aorta and pulmonary trunk produces persistent truncus arteriosus, while partial or aberrant division yields such defects as transposition of the great arteries or tetralogy of Fallot. Failure of the septal division of the primitive atrium leads to atrial septal defects.

It is during the period of organogenesis that the embryo is susceptible to the teratogenic effects of certain drugs or other substances, though it is estimated that only 10 % of all birth defects are due to a teratogenic agent per se. One example is the vitamin K antagonist warfarin, used widely as an anticoagulant. Maternal use of warfarin between the sixth and ninth menstrual weeks of gestation results in the warfarin embryopathy in an estimated 5–10 % of exposed embryos. This syndrome may include facial anomalies, skeletal anomalies, microcephaly, and mental retardation. Evidence is mounting that warfarin inhibition of arylsulfatase E activity is

involved in the teratogenesis of the drug. Use of warfarin later in pregnancy may also result in additional adverse fetal effects.

Critical organ developments occur in the fetal period. The fetal period begins at the end of the ninth or beginning of the tenth menstrual week. The embryo-fetus is about 4 cm long, all major organs are formed (though many are immature), and the skeletal structures are easily recognized. By the fourteenth week the sex of the fetus can be discerned by visual inspection of the genital region. Fetal lungs, formed by the seventh gestational week, undergo important branching and vascularization thereafter. The development of the gas-exchanging segments of the respiratory tree begins in the 22nd to 24th week and alveolar development continues into childhood. Survival outside the uterus is impossible before this time due to an inability to exchange oxygen and carbon dioxide. Rudimentary brain structures are in place by the end of the embryonic period, but the brain remains a smooth-surfaced structure for at least half of pregnancy, with gradual development of the mature pattern of gyral and sulcal folding occurring in an orderly sequence after 20 weeks gestation and into childhood. Cortical neurogenesis is not completed in the fetus until nearly 20 weeks gestation.

By 20 weeks, the fetus weighs about 300 g and some scalp hair may be found. A period of linear fetal growth begins, with glucose being the major fetal nutrient for oxidative metabolism and acquired via facilitated transport across the placenta. Amino acids and lactate are also used in aerobic metabolism by the fetus. Human placental lactogen in the mother's circulation impairs maternal tissue uptake of glucose, leaving it the circulation and available to the placenta (as well as predisposing to maternal glucose intolerance in genetically susceptible individuals). Free fatty acids, glycerol, and free amino acids also cross the placenta for use by the fetus. Fetal fat tissue deposition occurs primarily over the final third of pregnancy, increasing somewhat gradually from about 26 to 32 weeks and more rapidly thereafter. There is considerable interest today in environmental influences of fetal growth, especially by way of gene imprinting.

One of the most remarkable features of the fetal physiology is the fetal circulation. Fetal blood does not require oxygenation by the fetal lungs, and little fetal blood circulates through the pulmonary vascular circuit. Well-oxygenated fetal blood returns from the placenta via the umbilical *vein*, which divides into the ductus venosus and the portal sinus, with the ductus venosus being the major branch. These venous structures access the inferior vena cava high in the abdominal cavity in a way that favors the course of well-oxygenated blood flow along the medial aspect of the inferior vena cava in its return to the heart. When it reaches the right atrium, the configuration of the fetal upper atrial septum shunts the well-oxygenated blood through the patent fetal foramen ovale into the left ventricle from which it is directed to the systemic arterial circulation. Less well-oxygenated blood returning to the right atrium via the inferior and superior vena cava is deflected through the tricuspid valve to the right ventricle. Most blood ejected from the right ventricle courses through the ductus arteriosus, a fetal vessel connecting to the descending aorta. Only a small proportion of the right ventricular outflow is directed to the

relatively high-resistance pulmonary circulation. Right ventricular blood entering the descending aorta via the ductus arteriosus is carried back to the placenta via the fetal hypogastric arteries leading to the umbilical arteries.

Dramatic alterations to these uniquely fetal circulatory elements occur at birth: the umbilical vessels, ductus arteriosus, ductus venosus, and foramen ovale close or constrict. Expansion of the lungs at birth is associated with a dramatic decrease in pulmonary circulatory resistance. Right ventricular outflow preferentially follows the pulmonary circuit, to be oxygenated before its return to the left atrium. The adult circulation is established.

Maternal Physiologic Changes in Pregnancy

Cardiovascular System

Unique changes in maternal physiology occur in pregnancy to support the growing fetus and placenta and to protect the mother from blood loss at delivery. These changes are seen very early in pregnancy and normalize rapidly after delivery. Maternal plasma volume increases as early as 6 weeks, increasing 45 % and reaching a maximum of about 5,000 mL at 32 weeks. Red blood cell mass also increases roughly 20–30 % during pregnancy and is believed to be stimulated by progesterone, placental chorionic somatomammotropin, and possibly prolactin. Due to this disproportionate increase in plasma as compared to red blood cells, a physiologic anemia can be observed in the third trimester.

Anatomic changes to the entire cardiovascular system also occur. There is a softening of the smooth muscle and collagen as early as 5 weeks, likely mediated by vasodilatory effects of progesterone and nitric oxide. This results in mildly decreased blood pressure, which nadirs at 24–32 weeks and increases closer to term. These changes also result in a physiologic dilation of the heart, which along with an enlarging gravid uterus works to shift the cardiac axis anteriorly and to the left. This results in the appearance of an enlarged cardiac silhouette on chest X-ray. Although there is an increase in cardiac compliance, there is no change in ejection fraction.

Cardiac output increases by 30–50 % in pregnancy, half of which occurs by 8 weeks. The increase in cardiac output plateaus at 26–28 weeks [1]. This increase reflects an increase in both heart rate (by 15–20 beats per minute) and stroke volume (by 40 %) [2, 3]. Roughly 500–800 mL/min of blood is preferentially shunted to the uterus, ten times the requirement in a nonpregnant woman. Cardiac output can decrease up to 25–30 % when turning from a lateral recumbent to supine position due to gravid compression of vena cava. The most dramatic changes to cardiac output occur peripartum. Cardiac output increases 15 % in during 2nd stage with maternal expulsive efforts early labor, 25 % in active labor, and 50 % with maternal expulsive forces during the second stage of labor. Immediately after delivery, cardiac output can be expected to increase 80 % secondary to autotransfusion of the

blood previously sequestered in the uterus, but returns to pre-labor values by an hour after delivery [4].

Respiratory System

Maternal oxygen requirements increase 20–40 % to support the increase oxygen requirements of the fetus, placenta, and other maternal organs [5]. Elevated estrogen levels in pregnancy cause relaxation of the ligaments between the ribs and sternum, resulting in an increase in the subcostal angle and chest diameter. These changes along with the enlarging uterus contribute to an overall decrease in maternal oxygen reserve: 5 % decrease in total lung capacity and 20 % decrease in functional residual capacity. For this reason, women with pulmonary disease are more susceptible to early decompensation. However, there is 40 % increase in tidal volume. As respiratory rate does not change, there is a parallel increase in minute ventilation. Pregnancy is also a state of mild hyperventilation, mediated by progesterone to create a state of chronic mild respiratory alkalosis, which facilitates transfer of carbon dioxide from the fetus to the mother. The mean arterial pH is 7.43, and mean serum bicarbonate is 21.5 mEq/L [6–9]. The alkaline environment increases 2,3-diphosphoglycerate, which serves to favor oxygen transfer to the fetus. Normal blood gas values in pregnancy can be found in Table 2.1.

Hormonal changes of pregnancy also stimulate increased upper respiratory vascularity, mucosal edema, and mucosal secretion, which can predispose the woman to epistaxis, nasal congestion, upper airway obstruction, and even obstructive sleep apnea.

Renal System

Significant changes to renal anatomy and function occur during pregnancy. There is increased renal plasma flow during pregnancy, up to 75 % at 16 weeks and maintained until the third trimester after which there is a 25 % decline [10].

Table 2.1 Normal pregnancy blood gas

Arterial pH	7.44 (7.39–7.45)
PO_2	90–107 mmHg
PCO_2	25–33 mmHg
HCO_3^-	16–22 mEq/L

Modified from the 23rd edition of *Williams Obstetrics* (2010)

Likewise, there is a 50 % increase in glomerular filtration rate during the first trimester and maintained until the end of pregnancy; this results in decreased serum creatinine (average of 0.5 mg/dL) and urea (average of 9 mg/dL) [11]. There are also changes in renal tubular function and excretion of nutrients. Glycosuria is common in pregnancy, but typically intermittent and not necessarily reflective of serum glucose levels or gestational age. One study found that 90 % of pregnant women with normal serum glucose excreted 1–10 g of glucose per day in their urine [12]. However, repetitive findings of glycosuria should prompt screening for diabetes. Urinary excretion of protein and albumin is also increased in pregnancy, particularly in the second half of pregnancy but does not typically exceed 300 mg per 24 h.

Increased renal vasculature and interstitial volume result in an increase in renal size, up to 1 cm in length. There is also dilation of the collecting system, typically more pronounced on the right side (average of 15 mm) than the left (average of 5 mm) due to the dextrorotation of the gravid uterus and location of the sigmoid colon [13]. Dilation of the collecting system can be partially attributed to progesterone, which causes smooth muscle relaxation. These changes typically reverse by 6 weeks postpartum.

Gastrointestinal System

Elevated progesterone levels in pregnancy decrease gastrointestinal motility and gastroesophageal sphincter tone. These changes, along with uterine compression of the stomach, result in increased gastric reflux. Up to 80 % of pregnant women will have gastroesophageal reflux, and the prevalence and severity increases with increasing gestational age and resolves with delivery. Progesterone's relaxing effect on smooth muscle also decreases small intestinal peristalsis. Similar changes in colonic transit time are thought to occur and supported by animal studies. This increase in intestinal transit time may serve to increase nutritional absorption, but also contributes to constipation and bloating.

Little anatomic changes to the liver occur during pregnancy, with the exception of an upward shift, which corresponds to the upward shift of the diaphragm and growing uterus. There is a small decrease in the upper limit of aspartate transaminase and alanine transaminase [14]. Serum alkaline phosphatase increases two to fourfold during pregnancy, most of which occurs during the third trimester. Isoenzyme testing may be performed to distinguish placental production from liver or bone production of alkaline phosphatase. The increased alkaline phosphatase is mostly attributable to placental production of alkaline phosphatase, not hepatic production. Serum albumin and protein decrease throughout pregnancy, although this is largely due to hemodilution. Thus, any changes in liver enzymes, with the exception of alkaline phosphatase, should prompt further evaluation.

Other proteins produced by the liver are also increased during pregnancy. The concentrations of specific binding proteins such as corticosteroid-binding globulin and thyroxine-binding globulin also increase during pregnancy. There is also a two-fold increase in fibrinogen, and similar increase in factors VII, VIII, IX, and X. Levels of prothrombin and factor V remain relatively unchanged. Prothrombin time and activated partial thromboplastin time are not significantly changed.

Palmar erythema and spider angiomas, often seen with chronic liver disease, may also appear transiently in pregnancy due to increased levels of estrogen.

Muscloskeletal System

Pregnancy and lactation is a period of high bone turnover; both bone resorption and bone formation are increased throughout pregnancy, as is alkaline phosphatase, a marker for bone formation. However, this seems to be confined to trabecular bone and reversible with delivery and weaning of breastfeeding. There does not appear to be an association between increase parity and decreased bone marrow density or osteoporosis later in life [15, 16]. Pregnancy also results in several anatomic changes that predispose women to musculoskeletal discomfort during pregnancy. Increased pregnancy levels of estrogen and relaxin result in increased ligamentous laxity and increased joint discomfort throughout the body, particularly the pubic symphysis and sacroiliac joints [17]. To compensate for the growing uterus, there is an increasing lordosis of the lumbar spine to maintain the center of gravity over the woman's legs. The hyperlordosis of the lower back, increased pelvic joint laxity, and increased maternal weight cause opposing forces resulting in substantial mechanical strain on the lower back and pelvis. Lower back pain in pregnancy affects roughly two thirds of women and is likely worse for women with a history of back pain, prior pregnancy, or older age. The pain is usually exacerbated by physical activity, particularly weight bearing activity. Tenderness over the paraspinal muscles and sacroiliac joints is often appreciated on exam. Pain is often improved with postural and activity modification, and the prognosis is generally favorable.

Routine Pregnancy Features and Prenatal Care

Preconceptional Considerations

Ideally, the woman contemplating pregnancy will seek preconceptional education and take preventive care measures. Though not exhaustive, Table 2.2 outlines basic preconception recommendations, some of which are easily accomplished in a general medical practice setting.

Table 2.2 Basic preconception educational considerations and recommendations

	Consideration/recommendation	Comment
Prevention of fetal anomalies and syndromes		
Neural tube defects	Women of childbearing age who are capable of becoming pregnant should consume 0.4 mg of folic acid daily (available in multivitamin supplements)	Women with a previously affected child should consume 4 mg of folic acid daily from 4 weeks before conception through the first 3 months of pregnancy
Alcohol	Heavy drinking is a risk for fetal alcohol syndrome and should be avoided; most experts recommend avoiding any alcohol during pregnancy because no level of drinking is known to be safe	
Smoking	Smoking during pregnancy is associated with fetal growth restriction and increased perinatal morbidity and mortality due to placental abruption and preterm birth	Risks increase with the number of cigarettes smoked per day
Caffeine	Moderate caffeine consumption (<200 mg/day) is not thought to be associated with miscarriage, preterm birth, or fetal growth restriction	Consumption of more than 300 mg of caffeine per day may be associated with low birth weight
Sauna and hot tub exposure	Probably prudent to restrict sauna exposure to 15 min or less and hot tub to 10 min or less	Extensive animal data show hyperthermia is teratogenic and can cause neural tube defects; human data are scant
Methyl mercury	Theoretical concern of exposure in seafood has prompted FDA and EPA to recommend pregnant women to consume no more than 12 ounces of a variety of fish and shellfish per week	See www.fda.gov/Food/ResourcesForYou/ucm110591.htm
Vitamin A	Excessive consumption of vitamin A (more than 10,000 IUs per day) may be associated with fetal malformations	standard prenatal vitamins contain 4,000–5,000 IUs
Infection		
Rubella	Check titer and immunize susceptible nonpregnant women	Women should avoid becoming pregnant for 28 days after vaccination
Varicella	Check titer or immunize, depending upon history	Women should avoid becoming pregnant for 28 days after vaccination
Diphtheria	Immunize women who have not received immunization with past 10 years	May be given if pregnant or likely to become pregnant

(continued)

Table 2.2 (continued)

	Consideration/recommendation	Comment
Influenza	Recommended for all women who will be pregnant (in any trimester) during influenza season (October through March) because pregnant women are more severely affected than their nonpregnant counterparts	May be given if pregnant or likely to become pregnant
Hepatitis B	Immunize women at risk (having more than one sex partner during the previous 6 months, been evaluated or treated for an STD, recent or current injection drug use, or having had an HBsAg-positive sex partner)	May be given if pregnant or likely to become pregnant
CMV, listeriosis, toxoplasmosis, Parvovirus B19, HSV	Routine screening for immunity or infection not recommended	Prudent to discuss preventive measures, i.e., handwashing, gloves for changing cat litter or gardening, washing of produce and cutting boards with bleach, avoidance of raw or undercooked meats and raw eggs or unpasteurized dairy
Genetic conditions		
Carrier state screening	Screen appropriate populations for genetic disease carrier states such as Tay–Sachs disease, Canavan disease, cystic fibrosis, or hemoglobinopathies	
Medical conditions	Appropriate control of some medical conditions, such as diabetes mellitus, SLE, phenylketonuria, and hyperthyroidism, before conception can positively influence pregnancy outcome	
Obesity	Linked to higher rates of preeclampsia, diabetes, labor disorders, cesarean delivery, and peripartum complications	Weight reduction may improve pregnancy risks

For many women with rheumatic disease, important preconceptional considerations are the risks, if any, that pregnancy poses with regard to the interplay between their underlying rheumatic disease and pregnancy, as well as the risks their antirheumatic disease medications might pose to the fetus or pregnancy. These risks are discussed in detail in the relevant chapters of the text.

Diagnosing Pregnancy

Pregnancy is typically first recognized by a woman when she notices breast soreness or tenderness, fatigue, perhaps some nausea, and then misses her expected next menses. Of course, some women with established rheumatic disease will be tracking their potential for conception using widely available, over-the-counter ovulation test kits. These tests detect a surge of luteinizing hormone in urine as a predictor of ovulation within the following 24–48 h.

hCG is first detectable using sensitive tests in the urine and blood of pregnant women 8–10 days after conception (day 22–24 of a 28-day menstrual cycle). Concentrations of hCG rise rapidly in early pregnancy, peak at 9–10 weeks, and decline thereafter to a nadir at 20 weeks.

Establishing the Expected Date of Delivery (Dating the Pregnancy)

The duration of human pregnancy averages 280 days from the first day of the last menstrual period. This amounts to 10 lunar months, or about 9 calendar months. By historical convention, the first day of the last menstrual period is used to mark the "beginning" of pregnancy and gestational age is measured by menstrual weeks. This assumes a 28-day menstrual cycle with ovulation occurring on day 14; thus, this method of dating the pregnancy includes approximately 2 weeks that the woman was not actually pregnant. Nonetheless, obstetrical references to pregnancy duration, including those obtained by obstetrical ultrasound, are in terms of the convention of dating the pregnancy according to the last period.

Most pregnancies in the USA also are dated by ultrasound using standard biometric measurements of the crown-rump length in early pregnancy or a mathematically modeled composite of the measurements of the fetal head, abdomen, and femur in later pregnancy. Generally, and especially if the menstrual dates are uncertain, the ultrasound-determined dates trump menstrual dates when they differ by more than 3 days from 6 to 10 weeks, more than 5 days from 11 to 14 weeks, and more than 7 days from 15 to 20 weeks. Fetal size varies considerably as pregnancy advances such that measurement of the fetus is a less reliable tool for estimation of gestational age past the mid-second trimester and especially in the third trimester. Thus, the composite gestational age assessment has a variability (±2 standard deviations) in excess of 2 weeks beyond 30 weeks.

Initial Prenatal Visits and Laboratory Tests

The initial prenatal visit includes a history and physical examination as well as laboratory studies. Typical "prenatal labs" are shown in Table 2.3 and normal laboratory values for the pregnant woman can be found in Table 2.4. Though not required for good care, many practitioners obtain first or early second trimester fetal ultrasound to firmly establish the gestational age and due date. Accurate dating is critical to

Table 2.3 Typical routine prenatal evaluations of the first 20 weeks of pregnancy

Screening or diagnostic evaluation	Comment
Tests	
Prenatal "panel"	
Hemoglobin or hematocrit	Typically obtained as complete blood count
Blood type and Rh status	
Anti-erythrocyte antibody screen	A positive screen should prompt identification and titers of antibodies. Women who are Rh negative should have a repeat screen at 28 weeks prior to Rh immune globulin administration
Rubella titer	A negative titer is an indication for immunization after pregnancy—MMR vaccine is not recommended during pregnancy
RPR	False positive result is not uncommon among women with autoimmune disorders, particularly SLE
HBsAg	Used to detect chronic carriers of HBV
HIV	Routine screening (typically offered as an "Opt-out" test) and treatment recommended by ACOG; treatment significantly decreases rate of perinatal transmission
Other routine tests	
Pap smear	
Urine culture or assessment for urine nitrites and leukocytes esterase	Asymptomatic bacteriuria is more common during pregnancy and more likely to progress to pyelonephritis
Genetic tests	
Carrier screening based on racial and ethnic background	Screening may include testing for hemoglobinopathies, Tay–Sachs disease, Canavan disease, cystic fibrosis
Carrier screening based on family history	Screening may include testing for such conditions as fragile X syndrome and Duchenne's muscular dystrophy
Screening for trisomies 21, 18, 13	A combination of maternal biomarkers and/or ultrasound markers is typically offered to all patients; recently available maternal plasma cell-free fetal DNA for pregnancies at high risk for Down syndrome

obstetric decision-making and contributes to the reduction in unnecessary induction of labor for postterm pregnancy.

By the end of the first trimester, the new prenatal patient should be apprised of the risks of genetic conditions such as Down syndrome and of the available screening tests (Table 2.3) [18]. Within the last two decades, Down syndrome screening tests have evolved considerably, primarily because Down syndrome occurs in about 1 in 800 liveborns in the general obstetric population. The risk of Down syndrome and a number of other fetal chromosomal abnormalities increase with increasing maternal age due to increasing rates of meiotic nondisjunction. At a maternal age of 35 years, the risk of a Down syndrome birth is 1 in 385, and the risk of any feto-neonatal chromosome abnormality at birth is 1 in 204. By a maternal age of 40 these risks are 1 in 106 and 1 in 65, respectively.

Table 2.4 Normal reference ranges for the pregnant woman

	Normal pregnancy range
Hemoglobin	9.5–15.0 g/dL
White blood cell count	$(5.6–16.9)\times10^3/mm^3$
Platelets	$(7.7–10.4)\times10^9/L$
Sodium	129–148 mEq/L
Potassium	3.3–5.1 mEq/L
Chloride	97–109 mEq/L
Bicarbonate	20–24 mmol/L
Serum creatinine	0.5–0.7 mg/dL
Blood urea nitrogen	9–11 mg/dL
Serum bicarbonate	18–22 mEq/L
Uric acid	2.0–6.3 mg/dL
Fibrinogen	244–619 mg/dL
INR	0.8–01.05
Partial thromboplastin time, activated (aPTT)	24.2–38.9 s
Prothrombin time (PT)	9.5–13.5 s
Aspartate transaminase (AST)	3–33 IU/L
Alanine transaminase (ALT)	2–33 IU/L
Total bilirubin	0.1–1.1 mg/dL
Alkaline phosphatase	30–418 IU/L
Albumin	2.3–5.1 g/dL
Lipase	21–112 U/L
Amylase	15–83 g/dL
C-reactive protein CRP	0.4–20.3 mg/L
Erythrocyte sedimentation rate (ESR)	4–70 mm/h
C3 complement	62–111 mg/dL
C4 complement	18–36 mg/dL
Arterial pH	7.39–7.45
PO_2	90–107 mmHg
PCO_2	25–33 mmHg
HCO_3^-	16–22 mEq/L

Modified from 23rd edition of *Williams Obstetrics* (2010)

Invasive procedures enable direct testing of fetal cells for chromosomal abnormalities, but carry a risk of attributable fetal loss. Amniocentesis performed by experienced personnel as early as 15 weeks has a procedure-related loss rate as low as 1 in 400. Chorionic villus sampling may be performed as early as 9 weeks, but with a slightly higher loss rate than amniocentesis, although the difference is minimal in experienced hands. Though low, these risks have prompted the development of screening paradigms for fetal chromosomal abnormalities that enable targeting invasive procedures for women at higher than average risk. Among low risk patients, e.g., a 30-year-old patient without a suspicious history, who desires screening for fetal chromosomal abnormalities, screening paradigms using a combination of maternal age, maternal serum biochemical analytes (reflective of fetal-placental production), and fetal ultrasound findings may be used to establish a probability

that the fetus has a chromosomal abnormality such as trisomies of the 21,18, or 13 chromosomes [18]. The ultrasound aspect of the most commonly used Down syndrome screening paradigm is fetal nuchal translucency measurement at 11–13 weeks [6, 7]. An increase in nuchal translucency is an early presenting feature of a broad range of fetal chromosomal, genetic, and structural abnormalities. Using a 5 % false positive threshold, these screening paradigms provide a high "detection rate" for Down syndrome, though definitive diagnosis requires direct genetic testing of the fetus by such methods as amniocentesis.

More recently, the FDA has approved testing using cell-free fetal DNA in maternal blood as a *noninvasive* approach to Down syndrome screening in high-risk patients, e.g., a 40-year-old obstetric patient, as early as 10 weeks [19]. In high risk patients, this technology will detect more than 97 % of Down syndrome cases with a false positive rate of less than 0.5 %. It may perform similarly in low risk patients and studies are currently underway. This test likely performs similarly in low-risk women and studies in the population are currently underway.

Subsequent Prenatal Visits and Care

In healthy women without underlying medical conditions, subsequent prenatal visits are typically every 4 weeks until 28 weeks, every 2–3 weeks until 36 weeks, and then once weekly until delivery. These visits are used to assess the growth of the fetus by palpation of the uterus and measurement of the fundal height (done after 20 weeks), listen for a normal fetal heart rate, obtain periodic maternal blood pressure readings, and screen for urinary tract infection and proteinuria using urine dipsticks. After 20–22 weeks, the mother is also questioned routinely regarding fetal movement, with decreased fetal movement possibly indicating fetal compromise. Visits at 36 weeks and beyond allow for assessment of fetal presentation (cephalic, breech, or transverse) and appropriate management of presentations other than cephalic.

The now-standard, mid-trimester obstetric ultrasound at approximately 20 weeks is obtained with two primary goals in mind. First, fetal biometric measurements are used to confirm (or refute) the expected gestational age. Second, the fetal anatomy is assessed by way of well-established, standardized views of numerous fetal structures. The mid-trimester fetal anatomic survey does not, however, exclude more subtle defects such as mild-to-moderate stenotic lesions of the cardiac outflow tracts, less severe obstructions of the gut, isolated cleft palate, and a variety of other less visually dramatic anomalies. The standard mid-trimester fetal ultrasound also has no better than modest utility as a predictor of Down syndrome.

Most gestational age discrepancies found at the time of the mid-trimester ultrasound are due to uncertain menstrual dating information or longer than average menstrual cycles reflective of delayed ovulation. If the mid-trimester fetal biometric measurements do not agree with the menstrual gestational age or the gestational age established by an earlier ultrasound, common practice is to obtain another set of fetal measurements 3–4 weeks later in an effort to discern a meaningful pattern of fetal growth.

Universal screening for gestational diabetes mellitus (GDM) between 24 and 28 weeks gestation is recommended by most experts. In the USA, the orally

administered 50 g glucose challenge, with venous glucose drawn 1 h later, is the standard screening test. It may be prudent to perform the test earlier in patients at higher risk for gestational diabetes, such as obese women, women with a history of having delivered a previous large-for-gestational age infant, or women with a strong family history of type 2 diabetes mellitus. The most commonly used threshold for an abnormal result is a glucose of 140 mg/dL, though some choose to enhance sensitivity by using a lower threshold. Women who screen positive are recommended to undergo a 3-h oral glucose tolerance test using a 100 g oral glucose load. This test scheme involves a fasting glucose determination and additional determinations at 1, 2, and 3 h after the glucose load. A formal diagnosis of GDM is made when two or four determinations are above predefined thresholds, though women with a single abnormal result should also be considered at risk for worsening glucose tolerance as pregnancy advances.

Rh-negative women also have a repeat anti-erythrocyte antibody screen at 28 weeks. If negative for antibodies, the patient is a candidate for Rh immune globulin to prevent antepartum alloimmunization to possible fetal Rh positive cells. Note that the male partner's Rh status is most commonly unknown, but is assumed to be likely Rh positive based on known population blood type genetics. Additional Rh immune globulin is given to the Rh-negative, anti-erythrocyte antibody-negative mother soon after delivery if the neonate is confirmed Rh positive.

In otherwise normal women, prenatal visits after 20 weeks are thought to aid in the detection of fetal growth restriction and hypertensive disorders of pregnancy based on pertinent clinical inspections. Visits at 36 weeks and beyond allow for assessment of fetal presentation (cephalic, breech, or transverse) and appropriate management of presentations other than cephalic.

A sizeable proportion of women managed in an American obstetric setting undergo periodic fetal surveillance testing for evidence of placental insufficiency (see below) or fetal hypoxemia of other causes. By far, the most common fetal surveillance tests in routine use are the non-stress test (NST), assessment of amniotic fluid volume as an index (AFI), and the biophysical profile (BPP) test. Such testing has been a practice fixture since the 1970s (non-stress testing) and 1980s (AFI and BPP), though evidence of benefit is derived from retrospective and cohort studies; proper trials to are lacking.

The NST test uses a Doppler monitoring system to record a continuous fetal heart rate tracing and assumes that the presence of fetal heart accelerations with fetal movement is indicative of a neurologically intact brainstem-cardiac circuitry; the absence of these raises concern for severe impairment in maternal–placental circulation and severe fetal hypoxemia.

Amniotic fluid volume with AFI is normally in excess of 5 cm by 4-quadrant measurement; values below 5 cm are concerning for worsening maternal–placental circulation. Common indications for testing include maternal chronic hypertension or gestational hypertensive disorders, suspected fetal growth restriction, maternal diabetes, advanced maternal age, as well as autoimmune disorders such as systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APS).

More recently, analysis of in utero vascular Doppler velocimetry waveforms has been added to fetal surveillance testing for selected patients. The most commonly

used fetal vascular Doppler assessment is measurement of resistance to flow in the umbilical arteries, with evidence of increasing resistance to flow reflective of worsening maternal–placental circulation and the potential for worsening fetal oxygenation of the fetus. Randomized trials have been done for umbilical artery waveform analysis in some high-risk pregnancy populations, and the current Cochrane review concludes that this method of fetal surveillance in high-risk pregnancies reduced the risk of perinatal deaths and resulted in less obstetric interventions [20].

Mode of Delivery

Determining fetal presentation is a critical step in determining mode of delivery. The most common fetal presentation during labor is cephalic. Presentations not amenable to vaginal delivery are persistent breech and oblique or transverse lie. An attempt at rotating the fetus to cephalic with a procedure called external cephalic version may be made and if not successful, a cesarean is indicated. In rare cases where there is both an experienced provider and adequate maternal pelvis, a vaginal breech delivery may be attempted. Likewise, any anatomic malformation of the fetus that impedes flexion or extension of head such as a large neck mass would be an indication for cesarean delivery. Other fetal indications relevant to woman with rheumatic disease include fetal dysrhythmias not amenable to external fetal heart rate monitoring.

Other factors in determining mode of delivery include antenatal and intrapartum factors. Antepartum indications for a cesarean delivery include history of classical cesarean or uterine surgery involving the active portion of the uterus, two or more prior cesareans, placenta previa, placenta accreta spectrum disorders, and higher order multifetal gestation (three or more). Cesarean delivery may also be indicated in cases where obstetric complications require expedited delivery [such as acute fatty liver of pregnancy (AFLP), hemolysis, elevated liver enzymes, low platelets (HELLP), and severe preeclampsia] that is not likely to be achieved with vaginal induction given unfavorable clinical assessment of the cervix. Rarely is cesarean indicated for women with rheumatic or osteoarthritis unless passive hip abduction is not possible. Intrapartum indications for cesarean delivery include fetal distress, maternal distress, arrest of dilation, or arrest of descent. The latter two may reflect feto-pelvic disproportion. In cases of fetal macrosomia, commonly defined as estimated fetal weight is >4,500 g for the diabetic and >5,000 g for the non-diabetic woman, a cesarean may be offered given the significantly increased risk for shoulder dystocia.

Selected Pregnancy Complications

Some pregnancy complications are more common in women with rheumatic diseases, e.g., preeclampsia in women with SLE. A primer on selected pregnancy complications that are somewhat more likely to occur in women with rheumatic disease is offered below.

Pregnancy Loss

Human conception and pregnancy may be characterized as somewhat inefficient. Assisted reproductive technology programs find that well under half of preimplantation conceptions succeed. Overall, at least 30 % of human spontaneous pregnancies recognized by the presence of β-hCG, representing implantation, fail [21]. Most of these are lost before the missed menses that typically heralds the patient's recognition of pregnancy, but 10–15 % are lost after recognition of pregnancy, usually within the first 12 weeks of gestation. Among these, most fail in the pre-embryonic or embryonic periods, though the clinical features of miscarriage often do not ensue for up to several weeks. The fetal period is most commonly defined as beginning at 10 weeks, and the death of the conceptus in utero thereafter is a "fetal" death. Historically, pregnancy losses prior to 20 weeks gestation have been termed "miscarriages" or "spontaneous abortions," and the delivery of a dead fetus at or beyond 20 weeks has been referred to as "stillbirth." In the general obstetric population, fetal death occurs in some 1.5–2 % of pregnancies, with most of these occurring between the 10th and 15th week. From 16 weeks forward, approximately 1 % of live fetuses expire in utero [22]. After 20 weeks, fetal deaths occur in approximately 5–7 per 1,000 births in the general US population [23].

Within the general obstetric population, variables well recognized to influence pregnancy loss include maternal age and prior pregnancy loss. Pre-embryonic, embryonic, and fetal loss rates increase with increasing maternal age. Even among women with no prior pregnancy losses, the likelihood of pre-embryonic or embryonic loss per pregnancy exceeds 20 % by age 36 years and approaches 40 % by age 40 years. A sizeable proportion of these losses are aneuploidy conceptions, though certainly not all. Most pregnancy losses in the pre-embryonic or embryonic period go unexplained since chromosomal analysis of abortus tissue is not common practice.

Fetal deaths also are increased in relation to maternal age and prior fetal death, as well as with obesity, smoking, chronic hypertension, and black race [24]. Fetal deaths at or beyond 20 weeks are twice as likely in women more than 35–39 years of age compared to those less than 35 years of age and 1.5–3 times as likely in women with a prior stillbirth. BMI > 30, smoking more than ten cigarettes per day, chronic hypertension, and black race also are associated with a twofold increased risk compared to the general population. By comparison, insulin-requiring diabetes and SLE carry increased risks at least several fold higher than that of the general population.

Apart from the well-recognized associations with specific maternal condition such as diabetes or SLE, fetal death may be due to fetal infections, chromosomal abnormalities, syndromes of a Mendelian or polygenic origin, uterine malformations (e.g., uterine septum), or feto-maternal hemorrhage. Some experts hold that heritable thrombophilias may play a role in fetal death. A recently completed population-based study of fetal deaths at 20 weeks or later, with thorough maternal, fetal, and placental evaluations, found that fetal deaths were most commonly attributable to placental disease, infection, fetal genetic or structural abnormalities, or obstetric

complications (e.g., maternal hemorrhage). Importantly, the "placental disease" category includes histopathological lesions that are nonspecific in nature. Lupus anticoagulant and anticardiolipin were present in less than 5 % of women tested.

Intrauterine Growth Restriction

Fetal access to nutrients and gas exchange depends upon the development of an adequate maternal–placental–fetal circulation, with the villous trophoblast as the primary site of exchange. The placenta actively transports glucose, amino acids, and free fatty acids from the maternal to the fetal circulation. The rate of fetal growth accelerates at 24–28 weeks and slows somewhat at 32 weeks forward. However, most fetal fat gain occurs after 28 weeks and particularly after 32 weeks.

Pathologic restriction of fetal growth can be grouped into several categories, though overlap of these is common. Perhaps the most important etiology of intrauterine growth restriction (IUGR) is poor placental vascular development, a condition commonly termed "uteroplacental insufficiency" or more simply, "placental insufficiency." Placental insufficiency is easily the single most common cause of IUGR in singleton US pregnancies. It is also well known to be associated with maternal hypertensive or vascular conditions, including maternal renal disease of diverse etiologies ranging from acquired nephritis to inherited nephropathies. The mechanism of poor placental development leading to placental insufficiency is not well understood.

Other etiologies of restricted fetal growth include inherent conditions of the fetus, such as fetal chromosomal or genetic conditions and fetal infection. Low prepregnancy maternal weight or poor weight gain in pregnancy also are associated with impaired fetal growth, though these are not major contributors to IUGR in the USA. Maternal smoking, cocaine use, and alcohol use also are associated with IUGR.

Experts have identified two patterns of restricted fetal growth. Asymmetric IUGR entails restricted somatic growth with sparing of fetal head growth. Such fetuses have smaller abdominal circumference measurements with relatively normal head measurements. This is the type of IUGR most commonly seen with placental insufficiency. In symmetric IUGR, all fetal measurements are similarly reduced, including head measurements. Symmetric fetal growth restriction is typically associated with early insults, such as fetal genetic abnormalities or syndromes, or insults that impair growth in numerous organ systems, such as with certain viral infections.

Hypertensive Disorders of Pregnancy

Hypertensive disorders complicate up to 10 % of pregnancies in unselected obstetric populations and are a major cause of maternal and feto-neonatal morbidity and mortality. The two most common forms of hypertensive disorders of pregnancy are

Table 2.5 Criteria for severe preeclampsia

Blood pressure ≥160 mmHg systolic or ≥110 mmHg diastolic, recorded on at least two occasions at least 4 h apart with patient on bedrest
Progressive renal insufficiency (serum creatinine > 1.1 mg/dl or two times normal value)
New-onset cerebral or visual disturbances
Pulmonary edema
Severe persistent epigastric or right upper-quadrant pain
Impaired liver function (serum transaminase at least two times normal value)
Thrombocytopenia (<100,000 platelets/ML <100 $\times 10^9$/L)

Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013 Nov; 122(5):1122–31

gestational hypertension and preeclampsia, both of which are more common among women with SLE and among women with renal disease of virtually any etiology, including autoimmune.

Gestational hypertension and preeclampsia are vasospastic hypertensive disorders marked by abnormal maternal arteriolar reactivity to vasoactive agents such as prostacyclin, thromboxane A2, nitric oxide, and endothelins. The hallmark of gestational hypertension and preeclampsia is new elevation of blood pressure (BP) to more than a systolic of 140 mmHg or a diastolic of 90 mmHg *after 20 weeks gestation* and present on two more occasions at least 4 h apart. Such elevated BPs prior to 20 weeks most likely represent chronic hypertension.

Preeclampsia is distinguished from gestational hypertension by the presence of new proteinuria (≥0.3 g per 24 h, protein/creatinine ratio ≥0.3, or 1+ by dipstick) or any of several other clinical features representing maternal end-organ injury, including cerebral symptoms, serum urate >5.5 mg/dL, hemoconcentration, thrombocytopenia, hepatic dysfunction, or placental insufficiency resulting in fetal growth restriction. By definition, these maternal or fetal features are absent in gestational hypertension, though gestational hypertension develops into preeclampsia in at least 25 % of patients. Women with chronic essential hypertension are also predisposed to preeclampsia as manifest by worsening hypertension and other clinical features in the second half of pregnancy.

Preeclampsia exists on a continuum of severity and is generally described as either mild or severe (note that there is no "moderate" preeclampsia). Accepted criteria for the diagnosis of severe preeclampsia are shown in Table 2.5. Mild preeclampsia is defined as new-onset BP of 140–159 mmHg systolic and 90–109 mmHg diastolic and proteinuria of 0.3–4.9 g per 24 h.

The cause(s) and pathophysiological details of hypertensive disease of pregnancy remain unclear, in part because hypertensive disorders of pregnancy occur in a wide array of clinical situations, e.g., in normal nulliparous women, as well as in women with chronic renal disease and related hypertension. Many experts hold that the key event is abnormal trophoblast invasion, including suboptimal formation of the maternal–placental circulation (see IUGR above). Evidence points to varied factors such as imbalances in angiogenesis or coagulation, underlying

genetic predisposition to vascular hyperreactivity, increased oxidative stress, dysfunctional cardiovascular adaptation to pregnancy, and exaggerated inflammatory responses at the maternal–fetal interface. The latter may be particularly important to the predisposition to hypertensive disorders of pregnancy among certain autoimmune populations.

Regardless of the exact cause, inadequate placentation is established by 18–20 weeks of gestation and, depending upon the degree of inadequacy, can result in two major and often overlapping clinical features and their sequelae. The first is IUGR, discussed in the preceding section. The other is pregnancy-related hypertension. One popular and credible theory is that the feto-placental unit response to inadequate maternal–placental circulation is the elaboration of vasoactive substances that promote increased blood flow to the placenta. This works up to a point, but eventually in predisposed individuals results in adverse maternal vascular effects. These can include vasospasm-induced ischemia in cerebral, hepatic, and renal beds, as well as in the maternal–placental circulation.

The management of IUGR, gestational hypertension, and preeclampsia includes serial observation of the mother and fetus to detect evidence of more severe involvement requiring delivery. For the fetus, a typical observational plan would include "surveillance" using NSTs, amniotic fluid volume assessment, BPPs, fetal vascular Doppler assessment, or a combination of these. In most centers, twice weekly fetal assessment is standard.

Maternal observation is generally aimed at detection of severe preeclampsia (Table 2.5) and may be done as an outpatient or inpatient, depending upon the degree of concern. Ultimately, ongoing care of IUGR, gestational hypertension, and preeclampsia depends upon (1) the gestational age and (2) the severity of maternal or fetal disease. For practical purposes, pregnancies that have reached 36–37 weeks are candidates for delivery, even in the setting of mild fetal growth restriction or gestational hypertension.

For gestational ages less than 36 weeks, delivery decisions are influenced by the severity of disease as manifest by such parameters as the estimated fetal weight or the degree of oligohydramnios in fetal growth restriction and the degree of BP elevation or the presence of features of severe preeclampsia in hypertensive disorders. With infrequent exceptions at very early gestational ages, severe preeclampsia is an indication for delivery. In both IUGR and hypertensive disorders of pregnancy, abnormal fetal testing results suggestive of fetal hypoxemia are also an indication for delivery. Determining the mode of delivery involves consideration of gestational age, cervical evaluation, parity, and whether the woman is in labor. If these factors suggest a likely prolonged induction (>24 h), cesarean delivery may be reasonable. For gestational age $\leq$32 weeks, induction of labor is not likely to be successful, with only a third achieving vaginal delivery [25]. Conversely, induction of labor for gestational age $\geq$ 34 weeks will be successful for roughly two thirds of women [26].

It is worth noting that the treatment of gestational hypertension and preeclampsia with antihypertensives does little to influence disease progression or alter the timing of delivery. Medications such as hydralazine, labetalol, and nifedipine are, however, used to control severely elevated maternal BPs. Ultimately, the definitive treatment is delivery.

Table 2.6 Criteria for HELLP syndrome

Hemolysis
Abnormal peripheral smear
AND
Serum lactate dehydrogenase LDH > 600 IU/L
OR
Total bilirubin ≥ 1.2 mg/dL
Elevated liver enzyme
AST at least two times normal value
ALT at least two times normal value
Thrombocytopenia
Platelets < 100×10^9/L

HELLP syndrome is the presence of hemolysis, elevated liver enzymes, and low platelets and is considered a variant of severe preeclampsia. HELLP syndrome complicates 0.5–0.9 % of all pregnancies [27]. The most frequently used diagnostic criteria is the Tennessee Classification System (Table 2.6). Note that the diagnosis of HELLP does not require the presence of hypertension or proteinuria, though the former is present in all but the exceptional case. If only one or two of the three diagnostic criteria are met, some experts distinguish a "partial HELLP." Liver failure and coagulopathy is rare in HELLP syndrome, and such findings should prompt workup of other causes such as acute fatty liver or hepatitis. The development of significant nausea and vomiting, right upper-quadrant pain, or epigastric pain should prompt consideration of liver involvement and swelling. Although the development of subcapsular liver hematoma and/or liver rupture is rare (1 %) and not well understood, it can be dramatic and pose significant risk for maternal and fetal morbidity [28]. Similar to preeclampsia, delivery is the only definitive treatment. Though maternally administered non-fluorinated corticosteroids may improve the maternal platelet counts, such agents do not improve maternal or neonatal outcomes [29]. As HELLP syndrome is progressive with serious potential for rapid maternal deterioration, prompt delivery should follow the diagnosis but does not preclude vaginal delivery as long as vaginal delivery is likely to be successful in <24 h. Delay in delivery may be undertaken for completion of antenatal corticosteroid administration in cases of prematurity if continuous maternal and fetal monitoring ensures stable condition. Like severe preeclampsia, intravenous magnesium sulfate for seizure prophylaxis and antihypertensives for treatment of dangerously high blood pressure should be initiated.

Eclampsia is the occurrence of generalized tonic clonic seizure in the presence of proteinuria and hypertension and in the absence of other neurologic conditions. Although historically thought to be the final evolution of preeclampsia, eclampsia is simply but one of several manifestations of severe preeclampsia due to small arteriolar vasospasm and peripheral ischemia. It is not uncommon for eclampsia to be the first presentation of hypertensive disease. In the absence of magnesium seizure prophylaxis, eclamptic seizure will occur in 0.5 % of women with mild preeclampsia and 2–3 % of women with severe preeclampsia, and recurrent seizure will occur in 10 % of eclamptic women. Most seizures occur during the antepartum period,

followed in frequency by intrapartum and first 48 h postpartum periods, and will typically terminate spontaneously within 1–2 min. Fetal bradycardia during and immediately after the seizure is common and does not necessitate emergent cesarean delivery unless severe fetal compromise is apparent despite maternal and fetal resuscitation. The management of eclampsia should include protection of airway, maintenance of maternal oxygenation, delivery, treatment of any hypertension, and prevention of recurrent seizure.

Prevention of recurrent seizure is with administration of magnesium sulfate. Multiple trials have demonstrated that magnesium sulfate is superior to other antiepileptic medications, such as diazepam or phenytoin, for primary seizure prevention, seizure recurrence, and maternal death. Its use is associated with a 59 % reduction in seizure, a 36 % reduction in placental abruption, and a nonsignificant reduction in maternal mortality [30]. Magnesium seizure prophylaxis is typically given as a 4–6 g intravenous bolus over 15–20 min followed by a maintenance dose of 2 g/h continued through 24 h postpartum. Aggressive antihypertensive treatment should also be initiated as up to 20 % of eclamptic deaths are due to hypertensive stroke.

Eclampsia does not preclude vaginal delivery, although delivery should be expedited (<24 h). As with severe preeclampsia, determining the mode of delivery involves consideration of gestational age, cervical evaluation, parity, and whether the woman is in labor. If these factors suggest a likely prolonged induction (>24 h), cesarean delivery may be reasonable and is often the case for gestational age $\leq$ 32 weeks.

Preterm Birth

Historically, *preterm* birth is defined as birth after 20 weeks and before the completion of the 37th menstrual week of gestation. The rate of preterm birth in the USA is 12 %, a rate that is nearly twice as high as in Western Europe. In the USA, preterm birth accounts for over 85 % of all infant deaths in the USA and myriad of neonatal morbidities, respiratory distress syndrome, intraventricular hemorrhage, bronchopulmonary dysplasia, patent ductus arteriosus, necrotizing enterocolitis, sepsis, apnea, and retinopathy of prematurity. Long-term medical problems include chronic lung disease, neurodevelopmental disabilities, and visual and hearing impairment.

The major etiologies of preterm birth are preterm labor (PTL) with intact membranes, preterm premature rupture of membranes (PPROM) with subsequent labor or need for delivery, and indicated delivery for such complications as bleeding (e.g., from a placenta previa or placental abruption), severe preeclampsia, or other serious maternal or fetal conditions.

With regard to PTL and PPROM, numerous associations have been reported (Table 2.7). In particular, a history of prior spontaneous preterm birth is now well recognized as a major risk for recurrent spontaneous preterm birth.

Table 2.7 Some factors associated with singleton spontaneous preterm birth

- Genital and urinary tract infections
- Cervical disease, e.g. precancerous lesions, and treatment
- African American race
- History of a previous spontaneous preterm birth
- Uterine malformation
- Tobacco abuse
- Substance abuse
- Poor nutrition and low pre-pregnancy BMI
- Peridontal disease
- Low socioeconomic status
- Limited education

Table 2.8 Some indications for iatrogenic preterm delivery

- Hypertensive disease, chronic or gestational
- Placental disorders (previa, abruption, accreta)
- Maternal thrombosis or embolism
- Rheumatic diseases, e.g., SLE or APS
- Prior uterine surgery involving the upper uterus, e.g., prior classical cesarean or transmural myomectomy
- Poor fetal growth or oligohydramnios
- Fetal distress, e.g., abnormal fetal surveillance testing
- Fetal compromise as evident by imaging, e.g., fetal hydrops, fetal cardiac dysfunction, life-threatening fetal defect(s) or by other tests

Indicated preterm births occur for numerous reasons, but in general fall into categories of either serious maternal or serious fetal conditions for which delivery represents the best management option (Table 2.8). For indicated preterm births, of course, the gestational age is a key component of timing. Thus, for the mother on full anticoagulation because of recurrent thrombotic episodes, early delivery at 37 or 38 weeks might be a reasonable plan with regard to balancing maternal risks (spontaneous onset of labor while fully anticoagulated) against neonatal risks. On the other hand, severe preeclampsia at 28 weeks threatens the well-being of both mother and fetus and is not amenable to long delays in delivery.

Multifetal gestation, most commonly twins or triplets, is another important category of preterm birth. Twins and triplets are more frequent today than in the past due to assisted reproductive technology in infertility and are associated with higher rates of both dizygotic and monozygotic pregnancies. Multifetal gestations not only have higher rates of spontaneous preterm birth due to PTL and PPROM but also are more likely to develop complications requiring early delivery such as fetal growth restriction and preeclampsia. The average gestational age of twin and triplet deliveries in the USA is 36 and 32 weeks, respectively.

Among pregnancies threatening to delivery prematurely, the most important medical consideration is the use of fluorinated steroids administered to mother. Fluorinated steroids, unlike their unfluorinated counterparts, are less extensively

metabolized by placental enzymes and cross the placenta prior to birth and enhance fetal maturity, in particular pulmonary maturity. The most commonly used agent in the USA is betamethasone. Optimal neonatal benefit is achieved if delivery can be delayed for 48 h after administration of the steroid to the mother. Thus, if PTL is suspected, an agent to retard labor and delay delivery is often administered in conjunction with the steroid. The most commonly used agents in the USA are indomethacin and nifedipine. The former is little used after 32 weeks gestation because of adverse fetal effect (constriction of the ductus arteriosus). With PPROM, a course of amoxicillin-ampicillin and erythromycin may prolong pregnancy and reduce infection-related complications.

GI Disorders

Nausea and Vomiting of Pregnancy

Nausea and vomiting is a common problem in pregnancy, affecting 70–85 % of pregnant women [31]. The mechanism(s) of this very common gestational disorder remains uncertain, although elevated levels of estrogen and progesterone, gastric reflux, and decreased gastric motility may contribute. Onset is typically at about 6 weeks and resolves by 16 weeks. Nausea and vomiting in pregnancy exists as a continuum. At its extreme, the condition is known as hyperemesis gravidarum. Although there is no single standard diagnostic criteria for hyperemesis gravidarum, roughly 0.5–2 % of pregnant women are affected with a constellation of persistent emesis, dehydration, ketonuria, and weight loss. Management includes avoidance of triggers and small, frequent meals. Commonly used medications include vitamin B6, doxylamine, promethazine, metoclopramide, and ondansteron, though none are supported by robust clinical studies.

Gastroesophageal Reflux Disease

Gastric reflux is the most common gastrointestinal complaint in pregnancy, affecting 50–80 % of women by the third trimester. Diagnosis is clinical, and symptoms are same as those in nonpregnant women: epigastric burning or pain, nausea, dysphagia, regurgitation, vomiting, chronic cough, or asthma. Management is primarily lifestyle and dietary changes and medication. Avoiding dietary triggers, eating small low-fat meals, avoiding eating within a few hours of sleeping, and sleeping with the head of the bed elevated may be helpful. Pharmacologic therapy includes antacids and H2 receptor antagonists, both of which are safe in pregnancy, with the latter being FDA pregnancy category B. If symptoms persist, a proton pump inhibitor is typically added. All proton pump inhibitors are FDA pregnancy category B except for omeprazole, which is category C. If symptoms persist and are refractory to medical management, an upper gastrointestinal endoscopy may be considered, but is rarely needed.

Intrahepatic Cholestatis of Pregnancy

Intrahepatic cholestatis of pregnancy typically presents with pruritus starting in the second or third trimester. The incidence ranges from 0.1 to 15.6 % depending on geographic and ethnic variations, with increased frequency among Hispanics [32]. Pruritus is typically whole body, worse on the palms and soles, and peaks at night. There is no skin lesion present except as a result of excoriation. Intrahepatic cholestasis of pregnancy is associated with increased frequency of adverse obstetric outcomes including preterm delivery, intrapartum fetal distress, fetal death, and neonatal demise. It is not understood why fetal death occurs, although in rat models, impaired cardiac contractility and arrhythmias occurred with exposure to high levels of bile acids [33–35].

Diagnosis requires elevated bile acids greater than 10 μmol/L, the exclusion of other forms of liver disease, and resolution after delivery (symptoms typically resolve within 4 weeks after delivery). Other laboratory findings may include mildly elevated liver enzymes, bilirubin, and alkaline phosphatase. In 10 % of cases patients will be jaundiced. Ursodeoxycholic acid is considered the mainstay of treatment. It is associated with improvements in liver enzyme and bile acid parameters and is thought to reduce perinatal complications. As noted above, cases of unexplained intrauterine demise have been reported in cholestasis of pregnancy, typically after 36 weeks. Management with ursodeoxycholic acid and delivery by 37–38 weeks may improve outcomes [36–38]. Though of unproven efficacy, antenatal testing, such as with twice weekly NSTs, starting at 32–34 weeks gestation is usually recommended by experts.

Acute Fatty Liver of Pregnancy

AFLP is rare and a potentially life-threatening condition that affects 1 in 10,000 to 1 in 15,000 deliveries [39]. The onset is almost exclusively in the third trimester, with an average of 36 weeks [40]. AFLP appears to be associated with a defect in beta-oxidation of fatty acid and occurs in greater frequency among women who are heterozygous for long-chain 3-hydroxyacyl-enzyme deficiency (LCHAD) and carrying a fetus who is homozygous for LCHAD. Although the mechanism is not well understood, it is believed the mother is unable to sufficiently compensate for the fetal inability to metabolize fatty acids, resulting in liver damage. It typically manifests in the third trimester with 1–2 weeks of nausea, vomiting, abdominal pain, malaise, and anorexia. Laboratory values are significant for elevated liver enzyme, thrombocytopenia, hypoglycemia, and elevated ammonia. AFLP may be difficult to distinguish from HELLP, but AFLP is typically notable for severe hepatic insufficiency resulting in hypoglycemia, encephalopathy, and coagulopathy. Although definitive diagnosis is with a liver biopsy demonstrating microvesicular fatty infiltration of hepatocytes, this procedure is infrequently used in clinical practice due to its invasive nature and the typical presence of maternal coagulopathy. Thus, diagnosis is typically based on clinical and laboratory findings. Treatment is primarily

prompt delivery followed by maternal stabilization, typically in a critical care unit with a multidisciplinary team. Like preeclampsia, AFLP is not an indication for cesarean delivery; the mode of delivery should depend on the likelihood of a successful and timely vaginal delivery (<24 h) [39]. Patients will usually improve 2–3 days after delivery, although deterioration may continue for up to a week in some cases.

Venous Thromboembolism/Pulmonary Embolism

Pregnancy is a prothrombotic state. There is an increase in procoagulants such as von Willebrand factor, fibrinogen, and factors VII, VIII, IX, and X, a decrease in fibrinolytic factors such as plasminogen activator, and a decrease in the activity of some endogenous anticoagulant mechanisms such as protein S function and an increased resistance to activated protein C. There is also increased venous stasis due to compression of the vena cava by the gravid uterus and increased vascular compliance. Finally, vascular damage is inherently part of delivery, with the net effect of a particularly prothrombotic state in the postpartum period. The incidence of thrombotic events in pregnancy is about 1 in 1,000 women. About 50 % of these cases have an underlying genetic disorder. The diagnosis of VTE in pregnancy requires a high level of clinical suspicion.

Dermatologic Conditions in Pregnancy

Relatively common, benign dermatological changes of pregnancy include spider angiomas and teleangiectasia, palmar erythema, gingival hyperplasia, hyperpigmention (particularly of the areola and linea nigra), and postpartum "hair loss" (telogen effluvium). The latter is due to hormone-induced prolongation of the anagen phase of hair during pregnancy, with subsequent synchronized telogen phase after delivery.

Several pregnancy-specific dermatoses are to be distinguished. Pruitic urticarial papules and plaques of pregnancy (PUPPP) occurs in about 1 in 200 pregnancies. It usually affects primigravidae in the last weeks of gestation. The pruritic, polymorphic eruption tends to start within abdominal striae and characteristically spare the umbilicus. The papules coalesce into plaques that may spread to the buttocks and proximal thighs. Though small (2–4 mm) vesicles may form, blisters do not. Treatment with topical steroids and antihistamines is typically sufficient for control of the condition.

Atopic eruption of pregnancy, also known as prurigo of pregnancy, is a condition of eczematous or papular lesions typically with onset before the third trimester. A history of atopic dermatitis is found in many patients. The common features are eczematous lesions in common atopic sites and erythematous papules on the trunk and limbs. Atopic eruption of pregnancy may not be easily distinguished from PUPPP in many cases, but the treatment with topical steroids is the same.

Intrahepatic cholestasis of pregnancy, usually referred to cholestasis of pregnancy, is a fairly common cause of pruritus in later pregnancy. The skin itself appears normal, except as it might be affected by the patient scratching. Though the molecular cause is uncertain, the immediate cause of cholestasis of pregnancy is impaired excretion of bile salts resulting in elevated circulating bile acids. The itching often involves the palms and soles and becomes generalized ("everything itches"). Elevated serum bile acids are diagnostic. Hepatocellular enzymes and bilirubin are mildly elevated in some cases. Adverse fetal outcomes are associated with cholestasis of pregnancy and include an increased frequency of fetal death particularly in severe cases. Management aims to reduce circulating bile acids with ursodeoxycholic acid. Fetal surveillance testing and somewhat early delivery is recommended by many experts.

Pemphigoid gestationis (PG) is an infrequent autoimmune bullous disorder typically occurring in late pregnancy and the postpartum period. It is due to a complement-fixing autoantibody directed against an antigen in the hemidesmosomes of the dermal-epidermal junction. PG presents with marked pruritus associated with erythematous papules and plaques. The lesions usually begin on the abdomen and typically involve the umbilicus. They may, however, be widespread and include most skin surfaces in severe cases. Biopsy shows linear C3 deposition along the dermal-epidermal junction. Treatment is severity -dependent and includes topical steroids in mild cases and oral (or parenteral) steroids or other immunosuppressives in severe cases. Peri-delivery exacerbation is common. A small percentage of neonates will have blistering skin lesions secondary to passive transplacental transfer of the autoantibody.

Pre-pregnancy Assessment and General Obstetric Approach to the Pregnant Rheumatic Disease Patient

Women with rheumatic disease who are contemplating pregnancy should undergo preconceptional counseling with an obstetrician and rheumatologist in order to discuss maternal and fetal risks of pregnancy and if necessary to adjust her drug therapy in an attempt to maximize her disease management and minimize fetal harm (Table 2.9). For example, women with APS and prior thrombosis who are on warfarin should switch to heparin before 6 weeks gestation to avoid warfarin embryopathy (Table 2.9).

The risks of anti-rheumatic agents are discussed in full detail in Chap. 14.

Reproductive-aged women are disproportionately affected by rheumatic diseases, and in some cases an initial diagnosis is made in the course of an evaluation for adverse obstetric outcomes, e.g., diagnosis of APS after a 20 week fetal death. Systemic lupus and APS are unquestionably associated with an increased obstetric risk profile. This is especially true in patients with underlying hypertension, a history of renal disease, or a history of thrombosis. Preconceptional evaluation including laboratory testing can help establish baseline disease activity (Table 2.9).

Table 2.9 Recommended practices in pregnancies of women with systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), rheumatoid arthritis (RA), and systemic sclerosis (SSC)

Assessment/test	Preconception	First trimester	18–20 weeks	22–24 weeks	26–28 weeks	30–32 weeks	32–34 weeks	36–38 weeks
SLE								
Adjustments of drug therapy to minimize risks	X							
Laboratory assessments	X	X						
Antiphospholipid antibodies	X							
CBC with platelets	X							
Renal function and protein excretion (e.g., 24-h urine for CRCL and total protein)			X		X	X		
Screen for gestational diabetes[a]								
Obstetric ultrasound for fetal growth and amniotic fluid volume			X	X	X	X	X	X
Fetal surveillance tests[b]						X----------		
APS								
Adjustments of drug therapy to minimize risks	X	X[c]						
Laboratory assessments CBC with platelets	X	X X	X		X		X	
Assessment of anti-coagulation[d]								
Obstetric ultrasound for fetal growth and amniotic fluid volume			X	X	X	X	X	X
Fetal surveillance tests[b]						X----------		
RA								
Adjustments of drug therapy to minimize risks	X							

Obstetric ultrasound for fetal growth and amniotic fluid volume			X		X[e]	X	X	
Fetal surveillance tests[b]						X[f]----------		
SSC								
Adjustments of drug therapy to minimize risks	X							
Laboratory assessments								
Renal function and protein excretion (e.g., 24-h urine for CRCL and total protein)	X							
Obstetric ultrasound for fetal growth and amniotic fluid volume			X	X	X[e]	X	X	X
Fetal surveillance tests[b]						X[f]----------		

[a]Routine gestational diabetes screening is performed at 24–28 weeks gestation in otherwise low risk patients. However, for women on chronic glucocorticoids, earlier and more frequent screening is recommended

[b]May include NSTs, amniotic fluid volume assessment, BPPs, fetal vascular Doppler assessment, or a combination of these. Fetal surveillance testing is typically performed on a twice weekly basis, though practices may vary according to the degree of clinical concern

[c]If the patient is on warfarin, it should be discontinued before 6 weeks gestation to avoid warfarin embryopathy

[d]For women in whom full anticoagulation is the goal. Note that there is considerable variation in practice as to how often assessment of anticoagulation status is done. Women with lupus anticoagulant, which can prolong standard activated partial thromboplastin times should be assessed using anti-factor Xa assays, as should women on low-molecular-weight heparin agents

[e]The clinical utility of serial obstetric ultrasound to assess fetal growth and amniotic fluid volume in women with RA or SSc and an otherwise uncomplicated pregnancy is uncertain

[f]The clinical utility of fetal surveillance testing in women with RA or SSc and an otherwise uncomplicated pregnancy is uncertain

It is our practice to have all women with rheumatic disease followed closely by their rheumatologist during pregnancy, with the frequency of visits left to the discretion of the rheumatologist. Women with SLE, APS, and SSc are generally followed more frequently with visits at least every several weeks in early pregnancy.

At and beyond 20 weeks gestation, these patients are usually seen every 1–2 weeks for obstetric care, with primary goals of screening for gestational hypertensive disease and fetal growth impairment. With regard to the former, home blood pressure monitoring may be helpful; with regard to the latter, obstetric ultrasound examinations every 3–4 weeks are usually employed. Additional assessments, typically started after 26–28 weeks, may include fetal surveillance using NSTs, amniotic fluid volume assessment, BPPs, fetal vascular Doppler assessment, or a combination of these. Women taking chronic glucocorticoids are at increased risk for gestational diabetes and should be assessed for this condition, generally around 20, 28, and 32 weeks gestation (Table 2.9).

In contrast to SLE, women with otherwise uncomplicated RA do not typically require increased obstetric surveillance during pregnancy, and the same may be true in women with mild, stable SSc in the absence of cardiac, pulmonary, or renal involvement. Similarly, routine antenatal testing, including serial ultrasounds, NSTs, and BPPs are not necessary in these women and should generally be reserved for typical obstetric indications.

Conclusion

Significant changes in maternal physiology occur during pregnancy and may result in conditions similar to those suffered by women with underlying rheumatic disease. This overview of the obstetric patient serves to familiarize the rheumatologist with features of normal and complicated pregnancy. The following chapters build upon this understanding, addressing the nuances of pregnancy management in each specific rheumatologic disease.

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