# Clinical manifestations and diagnosis of early pregnancy

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## INTRODUCTION

The diagnosis of early pregnancy is usually based on measurement of human chorionic gonadotropin in urine or blood, but ultrasonography is also an accurate diagnostic technique. History and physical examination are not highly sensitive methods for early diagnosis.

Familiarity with the normal versus abnormal findings associated with early pregnancy is important in the medical care of reproductive-age females. This information can be helpful in alerting the clinician to the possibility of an abnormal pregnancy, such as ectopic pregnancy, or the presence of coexistent disorders. An impending miscarriage or ectopic pregnancy should be considered and excluded in any pregnant patient in the first trimester who presents with lower abdominal pain, bleeding, history of an ectopic pregnancy, an intrauterine device in place, or a history of tubal surgery (eg, tubal occlusion for permanent contraception, salpingectomy).

This topic will review the clinical manifestations and diagnosis of early pregnancy as well as signs and symptoms of concern. Miscarriage and ectopic pregnancy are nonviable pregnancies and are reviewed separately. (See "Pregnancy loss (miscarriage): Terminology, risk factors, and etiology" and "Ectopic pregnancy: Clinical manifestations and diagnosis".)

The safety of specific medications in pregnancy is discussed in topic reviews where the medications are used and in the Lexicomp drug interaction monographs for each drug.

## PHYSIOLOGY OF NORMAL PREGNANCY

Most of the clinical findings associated with normal pregnancy can be attributed to end-organ effects of the hormonal and mechanical changes associated with pregnancy. These pathophysiologic changes are described in detail separately:

- (See "Maternal adaptations to pregnancy: Cardiovascular and hemodynamic changes".)
- (See "Maternal adaptations to pregnancy: Dyspnea and other physiologic respiratory changes", section on 'Physiologic pulmonary changes in pregnancy'.)
- (See "Maternal adaptations to pregnancy: Renal and urinary tract physiology".)
- (See "Maternal adaptations to pregnancy: Gastrointestinal tract".)
- (See "Maternal adaptations to pregnancy: Hematologic changes".)
- (See "Breast development and morphology", section on 'Pregnancy and lactation'.)
- (See "Maternal adaptations to pregnancy: Musculoskeletal changes and pain".)
- (See "Maternal adaptations to pregnancy: Skin and related structures".)
- (See "Immunology of the maternal-fetal interface".)

## CLINICAL MANIFESTATIONS OF EARLY PREGNANCY

**Presentation** — Amenorrhea is the cardinal presenting symptom of early pregnancy. Pregnancy should be suspected in any female in their childbearing years who notes that a week or more has passed without the onset of an expected menses. Clinical suspicion is increased if they also report any sexual activity while not using contraception or with inconsistent use of contraception. However, even patients who report consistent use of contraception may become pregnant because of user issues and because no method is 100 percent effective ( table 1). Denial of sexual activity does not exclude pregnancy since sexual behavior is not always reported accurately [1].

Cessation of menses can be a difficult symptom to evaluate because some females have irregular menstrual cycles and many have occasional prolongation of a cycle. Furthermore, vaginal bleeding/spotting is relatively common in early normal pregnancy and often occurs at or near the time that a menstrual period would be expected [2,3]. In one prospective study, 14 out of 151 participants (9 percent) experienced at least one day of vaginal bleeding during the first eight weeks of pregnancy [3]. Bleeding tended to occur around the time they expected their period to occur and was typically light (requiring only one or two pads or tampons in 24 hours). (See "Evaluation and differential diagnosis of vaginal bleeding before 20 weeks of gestation".)

**Signs and symptoms** — The most common signs and symptoms of early pregnancy are:

- Amenorrhea
- Nausea with or without vomiting
- Breast enlargement and tenderness
- Increased urinary frequency without dysuria
- Fatigue

Additional signs and symptoms may include:

- Mild uterine cramping/discomfort without bleeding
- Abdominal bloating
- Constipation
- Heartburn
- Nasal congestion
- Shortness of breath
- Food cravings and aversions
- Mood changes
- Lightheadedness
- Spider angiomas
- Palmar erythema
- Increased skin pigmentation (face, linea alba, areola)
- Difficulty sleeping
- Low back pain
- Adnexal discomfort

In a study that prospectively collected data on the onset of pregnancy symptoms in 221 females attempting to conceive, 60 percent experienced some signs or symptoms of pregnancy as early as 5 to 6 weeks of gestation (ie, five to six weeks after the first day of their last menstrual period [LMP]), and 90 percent were symptomatic by 8 weeks [4]. Their symptoms tended to develop abruptly and occur daily. However, the symptoms were nonspecific: they also occurred in 9 percent of nonpregnant cycles.

**Findings on physical examination**

- The pregnant uterus is more globular than in the nonpregnant state and enlarged, increasing in size by approximately 1 cm per week after 4 weeks of gestation. The correlation between uterine size and gestational age is often described in terms of fruit (eg, 6 to 8 week size = small pear; 8 to 10 week size = orange; 10 to 12 week size = grapefruit). The uterus remains a pelvic organ until approximately 12 weeks of gestation when it becomes sufficiently large to palpate abdominally just above the symphysis pubis, unless the patient has obesity. At 16 weeks, the uterine fundus is palpable midway between the symphysis pubis and umbilicus. (See "Prenatal

assessment of gestational age, date of delivery, and fetal weight", section on 'Uterine size'.)

- The uterus and vaginal portion of the cervix soften beginning at approximately 6 weeks of gestation. Softening of the isthmus (lower portion of uterus adjacent to the cervix) allows the body of the uterus to flex against the cervix.
- The mucous membranes of the vulva, vagina, and cervix become congested and may appear bluish (Chadwick sign) beginning at approximately 8 to 12 weeks of gestation.
- The breasts become fuller and may become tender. The areola darkens, and the veins under the breast skin become more visible.
- Fetal cardiac activity can usually be detected by a handheld Doppler device at 10 to 12 weeks of gestation and sometimes earlier if the patient is thin and the clinician is persistent (fetal heart size is <7 mm at 10 to 12 weeks [5]).

## Laboratory findings

### Human chorionic gonadotropin

- **When is hCG first detectable? –** Detection of human chorionic gonadotropin (hCG) in blood or urine is the basis of all pregnancy tests ( table 2) (see 'Detection of human chorionic gonadotropin' below). hCG is secreted into the maternal circulation after implantation, which may occur as early as 6 days after ovulation but typically occurs 8 to 10 days after ovulation (ovulation occurs around day 14 of a 28-day menstrual cycle) [6-9]. This is the earliest that hCG can be detected with a standard serum hCG test. However, the ovulation-to-implantation interval has been observed to vary by up to six days in naturally conceived pregnancies [6]. Late implantation delays the time to a positive pregnancy test and has been associated with an increased risk of pregnancy loss [6,10].

  In a study of females with normal menstrual cycles who were attempting to conceive, the median hCG concentration on the first day of expected but missed menses (ie, approximately 4 weeks of gestation) was 239 milli-international units/mL in serum and 49 milli-international units/mL in a spot urine, but there was a wide range among individuals [11,12]. The range of hCG values was narrower in a study of over 4400 females who conceived by in vitro fertilization, underwent embryo transfer two to three days after egg retrieval, and had at least one viable embryo at 8 weeks of gestation: the median hCG concentration on day 12 after embryo transfer/day 16 after ovulation (ie, approximately 4 weeks of gestation) was 118 milli-international units/mL (interquartile range 98 milli-international units/mL) [13].

- **How does hCG level change across pregnancy** – The hCG concentration doubles every 29 to 53 hours during the first 30 days after implantation of a viable, intrauterine pregnancy; a slower rise is suggestive of an abnormal pregnancy (eg, ectopic, early embryonic death). (See "Ectopic pregnancy: Clinical manifestations and diagnosis", section on 'Human chorionic gonadotropin'.)

  The hCG concentration peaks at 8 to 10 weeks of gestation, averaging 60,000 to 90,000 milli-international units/mL at that time, but again, the range of normal is quite wide (5000 to 150,000 milli-international units/mL or more); thus, hCG levels are not useful for estimating gestational age [7,14-21], except in the first one to three weeks postconception [22,23] (see 'Detection of human chorionic gonadotropin' below). After 8 to 10 weeks of gestation, hCG levels decline, reaching a median concentration of approximately 12,000 milli-international units/mL at 20 weeks, again with a wide range of normal: 2000 to 50,000 milli-international units/mL or more [24]. hCG concentration stays relatively constant from approximately the 20$^{th}$ week until term.

  The factors accounting for the wide variation in interindividual hCG levels have not been studied extensively in accurately dated pregnancies; maternal weight accounts for some of the variation throughout pregnancy [25,26]. In some cases, an unrecognized vanishing twin affects the hCG level [27]. (See "Twin pregnancy: Overview", section on 'Vanishing twins'.)

**Other laboratory findings** — Numerous physiologic changes occur during pregnancy, sometimes accompanied by changes in laboratory test values ( table 3). One diagnostically important change is an increase in the neutrophil count, which begins in the second month of pregnancy and should not be mistaken for the leukocytosis associated with inflammation/infection. Pregnancy-related leukocytosis is not associated with an increase in percentage of band forms. (See "Normal reference ranges for laboratory values in pregnancy".)

**Ultrasound examination** — On transvaginal ultrasound examination, the timing of the first appearance of gestational landmarks based on LMP are as follows:

- **4.5 to 5 weeks** – Gestational sac or intrauterine fluid collection compatible with pregnancy
- **5 to 6 weeks** – Yolk sac ( image 1), which remains until approximately 10 weeks
- **5.5 to 6 weeks** – Embryonic cardiac activity
- **6 to 7 weeks** – Measurable embryo ( image 2)

These structures are observed slightly later with transabdominal ultrasound examination.

Biometric measurements (eg, crown-rump length, biparietal diameter) are used to estimate the gestational age (ie, duration of pregnancy) and delivery date. (See "Prenatal assessment of gestational age, date of delivery, and fetal weight".)

In one retrospective study, the lowest hCG level at which a gestational sac was visualized in a viable intrauterine pregnancy was 390 milli-international units/mL [28]. The threshold values for yolk sac and fetal pole visualization were 1094 milli-international units/mL and 1394 milli-international units/mL, respectively.

## DIAGNOSIS

The diagnosis of pregnancy is based on the presence of any of the following:

- Detection of human chorionic gonadotropin (hCG) in blood or urine
- Identification of pregnancy by ultrasound examination
- Identification of fetal cardiac activity by Doppler ultrasound

Several studies have examined the value of patient history for diagnosing early pregnancy ( table 4) [29-36]. Although patient report of delayed menses, sexual activity with imperfect use of contraception, and patient suspicion of pregnancy are predictive that a pregnancy test will be positive, these factors are not sufficiently reliable to diagnose or exclude pregnancy. Nausea with or without vomiting, if present, increases the likelihood of pregnancy, but some individuals do not experience these symptoms or merely have not experienced them before being tested.

Only a few studies have examined the value of physical examination for diagnosing early pregnancy ( table 4) [30,35,36]. The likelihood of pregnancy increases if signs of pregnancy are present, but absence of these signs does not rule out pregnancy. Obviously, the ability to detect physical signs of early pregnancy is highly dependent upon the experience of the examiner. (See "The gynecologic history and pelvic examination".)

**Detection of human chorionic gonadotropin** — The number of days after the last menstrual period (LMP) before a pregnancy test becomes positive depends on several factors, including [37,38]:

- Cycle length, which varies because the length of the follicular phase, and thus the timing of ovulation, varies by three to five days (or more) from cycle to cycle.
- The hCG assay's detection limit (ability to measure hCG at levels below 2 milli-international units/mL) and reference range cutoff (ie, threshold for a positive test), which differ for serum versus urine tests.

- The hCG assay's combination of antibodies to hCG isoforms.

Ovulation can occur as early as 8 days after the first day of the LMP; in such patients, hCG may be detected in serum on day 14 and in urine on day 16 of the cycle [7-9,39,40]. However, pregnancy tests are most likely to be positive at the time of the expected period [41].

As discussed above (see 'Human chorionic gonadotropin' above), the normal range for hCG concentration across most of the first trimester is quite wide; thus, hCG levels are generally not useful for estimating gestational age [7,14-21] except in the first one to three weeks postconception. Very early in gestation (ie, the first one to three weeks postconception), the rise in hCG levels is similar among patients with viable pregnancies at the same gestational age and allows estimation of pregnancy duration [22,23]. A study using a home-based urine testing device (Clearblue Advanced Pregnancy Test with Weeks Estimator) was able to estimate time since ovulation (one to two weeks, two to three weeks, three or more weeks) in singleton viable pregnancies with an accuracy of 93 percent when compared with standard reference methods using ultrasound and assessment of ovulation day [22].

**Types of pregnancy tests** — Pregnancy tests can be performed on urine or serum. Factors that influence the choice of a urine or serum pregnancy test include duration of missed menses, need to know the precise hCG level, convenience, and cost. Tests on urine are adequate for diagnosis of a suspected pregnancy in patients who have missed a menstrual period, especially when there is time to follow-up an initial negative test with a second test a week later. Because urine tests do not detect very low levels of hCG that would be detected by a serum test, a urine test may be negative and the serum test positive around the time of missed menses; therefore, serum tests are preferable when the patient's menstrual period is less than a week late, especially when exclusion of pregnancy is an important factor in patient care, such as before administering a potentially teratogenic agent.

**Serum pregnancy test** — In clinical practice, the serum pregnancy test is the most sensitive method for detecting hCG in early pregnancy. Serum pregnancy tests typically detect hCG levels as low as 1 to 2 milli-international units/mL; however, most laboratories report a pregnancy test as negative if the hCG level is <5 milli-international unit/mL, which is a well-established upper reference limit for nonpregnant females. Some laboratories report hCG levels ≤5 milli-international unit/mL as a negative pregnancy test [42]. Urine pregnancy tests are less sensitive because the median hCG concentration is lower in urine than in serum and they typically do not detect hCG until the level in urine is at least 20 milli-international units/mL [20,43]. Therefore, very early in pregnancy, a serum pregnancy test may be positive while the urine pregnancy test is still negative, as previously stated.

The only potential advantage of a qualitative serum pregnancy test over a quantitative test is that the qualitative test can usually be performed more rapidly [44]. The quantitative test procedure requires use of dedicated automated measurement equipment and may be

processed only in a commercial or hospital-based laboratory. It takes approximately 15 minutes to complete a test, but because samples are typically processed in batches, it may take much longer to obtain a result.

When a quantitative serum test is performed, most patients with singleton pregnancies will have a peak value <100,000 milli-international units/mL. Therefore, if a higher hCG level is noted, an ultrasound examination is indicated to exclude a multiple gestation or gestational trophoblastic disease, which could account for the finding.

**Urine pregnancy test —** Urine pregnancy testing is the most common method for diagnosing pregnancy. A variety of affordable and reliable qualitative urine tests are available and take only one to five minutes to perform.

Standard urine pregnancy tests used in clinical practice have a urine hCG threshold of 20 to 50 milli-international units/mL for a positive test. Because the urine hCG concentration can be much lower than in serum and urine tests require a higher hCG level to detect the hormone, urine pregnancy tests may not be positive when the serum pregnancy test is positive, as previously stated [45]. At eight days postconception, the serum hCG concentration may be 10 milli-international units/mL, whereas urine hCG concentration may still be less than 1 milli-international unit/mL [23,46,47].

A random urine sample can be used for testing because hCG production is not circadian [48-50] and a low urine-specific gravity does not appear to alter the sensitivity of detecting hCG unless the test used has a high threshold for hCG positivity [51,52] or the urine specimen is extremely dilute.

A semiquantitative multilevel urine pregnancy test has been developed that measures hCG levels in concentrations of <25, 25 to 99, 100 to 499, 500 to 1999, 2000 to 9999, and >10,000 milli-international units/mL. It is not more useful than a standard urine qualitative test for routine diagnosis of pregnancy. It was developed primarily for follow-up of patients after first-trimester medication abortion and monitoring after treatment for ectopic pregnancy.

**Home pregnancy test —** Home pregnancy tests (HPTs) are generally highly accurate, but positive results should be confirmed, such as with Doppler confirmation of fetal cardiac activity, sonographic visualization of the pregnancy, an enlarged uterus on physical examination, or a serum or urine hCG test performed by a clinician.

Individuals choose to use HPT kits because they are convenient and results are available quickly. Use of HPT kits is associated with earlier pregnancy confirmation, which can be beneficial. Barriers to HPT use, particularly among adolescents, include wanting to wait to see if menses begin, fear of the result, and wanting time to think about what to do if pregnant [53].

Many brands of HPT kits are available and generally detect hCG in the urine using immunometric assay methods [12]. The tests are interpreted by noting the number of color bands/lines in the window of the device a few minutes after dipping it in urine for several seconds. A positive test will show two band/lines (eg, "ll" or "+"), while a negative test only shows one band/line (eg, "l" or "-"). Some devices have a digital display that shows "yes" or "no" or "pregnant" or "not pregnant" on an LCD screen.

- **Accuracy** – Test performance is affected by the users' technique and interpretation [47,54]. Furthermore, although manufacturers claim these kits are 99 percent accurate, this claim is based upon the ability of the test to detect an arbitrary amount of intact hCG added in vitro to urine samples from nonpregnant females. In many cases, it will not be sufficiently sensitive to diagnose pregnancy in females who have recently missed a menstrual period.

  The most common problem with HPT kits is a "false" negative result because the test was performed too soon after the expected onset of menses. The intervals between the first day of the LMP, ovulation, fertilization, implantation, and production of sufficient hCG for detection by an HPT are variable. If pregnancy is suspected despite a negative test, the test should be repeated in one week. Many HPT kits make this recommendation and provide an extra kit for this purpose.

  HPT kits vary in sensitivity for detection of hCG; some do not detect levels below 100 milli-international units/mL [47,55]. This variability was demonstrated by a blinded in vitro sensitivity analysis of six commonly used HPT kits that found the following [56]:

  - First Response manual and First Response Gold digital devices were the most sensitive HPT kits with analytical sensitivity 5.5 milli-international units/mL. Over 97 percent of pregnancies could be detected on the first day of a missed period.
  - The next tier of tests had analytical sensitivity 11 to 22 milli-international units/mL.
    - EPT manual and digital devices detected 54 and 67 percent of pregnancies, respectively, on the first day of a missed period.
    - Clearblue Easy manual and digital devices detected 64 and 54 percent of pregnancies, respectively, on the first day of a missed period.

  Practitioners can use these data to advise their patients on selection of HPT kits and their limitations.

**Causes of a false-negative test**

- Performing the test too soon – The most common cause of a falsely negative pregnancy test is performing the test too soon after conception ( table 2). The test is

negative because ovulation (and thus fertilization, implantation, and first day of the missed menstrual period) occurred later than expected [57,58].

If pregnancy is suspected despite a negative test, the test should be repeated in one week. Waiting a week or two after a missed period before performing a urine pregnancy test not only minimizes false negatives, but also decreases the tendency to perform a serum hCG test to exclude or confirm very early pregnancy after a negative urine test. Individuals with irregular cycles or an uncertain LMP should generally wait at least 14 days from the most recent sexual act before obtaining a pregnancy test.

- Hook effect – Rarely, false-negative results are due to a "hook effect." When a very high hCG concentration is present and the sample is tested without prior dilution, both the capture and tracer antibodies used in immunoradiometric assays become saturated, preventing the binding of the two to create a sandwich. Since the non-sandwiched tracer antibodies are washed away with the excess material, the test result will be negative. This is most commonly seen with the very high hCG levels associated with gestational trophoblastic disease; hCG levels are generally lower in normal pregnancies. (See "Human chorionic gonadotropin: Biochemistry and measurement in pregnancy and disease", section on 'High-dose hook or prozone effect'.)

- Variant hook effect – An assay's inability to recognize specific isoforms of hCG can also play a role in false-negative results [38,59-61]. In early pregnancy serum, hCG consists predominantly of intact hCG (>95 percent) together with minor amounts of the free beta-subunit of hCG, the proportion of which may be up to 10 percent during the first weeks of pregnancy, decreasing to approximately 0.5 to 2.0 percent after the eighth week [62]. In urine, however, a large proportion of hCG is a metabolic fragment of the hormone known as the beta-core fragment of hCG. The beta-core fragment of hCG can interfere with urine tests that measure regular intact hCG because the beta-core fragment of hCG may saturate the binding capacity of either tracer or capture antibody, leading to falsely negative test strip results, most commonly at 7 to 12 weeks of pregnancy [61]. This has been called a "variant hook effect" or "hook-like effect."

In a series of 40 emergency department patients in which the urine hCG test was negative and the serum quantitative hCG was positive, the overall false-negative rate was 0.34 percent (40/11,760) [59]. In 18 of the 40 cases, the serum hCG level was below the detection limit in urine; the other 22 cases were considered false negatives due to a hook effect.

In a review of the US Food and Drug Administration Manufacturer and User Facility Device Experience (MAUDE) database from 1996 to 2014, of 707 cases of false-negative urine hCG test results, 142 (20 percent) were attributed to the variant hook effect from beta-core fragment of hCG, and 132 (19 percent) were attributed to performing the urine test before the limit of detection (which was defined as LMP four to six weeks before the false-negative

test, gestational age 4 to 6 weeks by ultrasound, and/or concurrent serum hCG concentration <200 milli-international units/mL) [63].

**Causes of a false-positive test —** Modern immunoassays for hCG, whether in urine or serum, specifically bind to the beta-subunit of hCG, thus preventing cross-reaction with subunits of other hormones, such as luteinizing hormone, follicle-stimulating hormone, and thyrotropin.

False-positive pregnancy tests are rare and due to:

- Operator error in performing or interpreting the test, particularly with HPTs.
- Biochemical pregnancy (ie, pregnancy loss very soon after implantation and before signs of pregnancy are apparent on ultrasound).
- Exogenous hCG administered as part of infertility treatment or for athletic performance. Exogenous hCG should be cleared by two weeks postinjection.
- hCG secretion from a tumor.
- Pituitary hCG secretion, typically in perimenopausal and postmenopausal females.
- Interference with the assay by anti-animal antibodies, anti-hCG antibodies, or other substances (eg, high doses of biotin may cause a positive serum test, but a urine test is usually negative).
- Familial hCG syndrome (a very rare genetic condition).

Medications do not cause false-positive pregnancy tests, unless the medication contains hCG or, rarely, certain antibodies.

The characteristics, causes, and evaluation of false-positive pregnancy tests are discussed in detail separately. (See "Human chorionic gonadotropin: Biochemistry and measurement in pregnancy and disease", section on 'Analytical causes of erroneous results; antibody-related interference'.)

## POSTPREGNANCY TEST CONSIDERATIONS

When human chorionic gonadotropin (hCG) is initially detected, the provider needs to think about the following:

- Is the pregnancy intrauterine or extrauterine?
- If intrauterine, is the pregnancy viable?
- What are the patient's feelings about the pregnancy?

**Determining pregnancy location** — All females with a positive hCG test can be offered an appropriately timed ultrasound to assess for a viable intrauterine pregnancy and to confirm or revise the expected date of delivery based on the last menstrual period. Because 98 percent of pregnancies are intrauterine, the pregnancy is generally assumed to be intrauterine **unless** the patient has one or more of the following:

- Adnexal pain
- Vaginal spotting/bleeding
- Risk factors for an extrauterine pregnancy ( table 5)

In patients at increased risk of ectopic pregnancy, the possibility of an extrauterine pregnancy can almost always be excluded by demonstrating an intrauterine pregnancy by transvaginal ultrasound examination [64]. However, ultrasound may not detect an intrauterine pregnancy before 5 weeks of gestation or at a serum hCG concentration below the discriminatory cutoff (eg, 3510 milli-international units/mL), though the discriminatory zone varies by laboratory and institution. (See "Ectopic pregnancy: Clinical manifestations and diagnosis", section on 'hCG discriminatory zone'.)

In a patient with a positive pregnancy test and a transvaginal ultrasound that shows neither an intrauterine pregnancy nor an ectopic pregnancy (ie, pregnancy of unknown location), serum hCG is tested serially to determine the rate of rise. An abnormally slow rate of rise suggests either an ectopic pregnancy or a pregnancy that will eventually miscarry. The correlation between ultrasound findings, absolute hCG level, and change in hCG level over time for diagnosis of viable versus nonviable intrauterine pregnancy versus an ectopic pregnancy is complicated and reviewed in detail separately. (See "Approach to the patient with pregnancy of unknown location".)

**Determining viability** — An intrauterine pregnancy can be assumed to be viable except in patients who report vaginal bleeding with or without suprapubic pain/cramping and/or cessation of symptoms associated with early pregnancy. For these patients, transvaginal ultrasonography is indicated to look for embryonic/fetal cardiac activity, which confirms viability.

In patients who have an initial transvaginal ultrasound very early in pregnancy that demonstrates an intrauterine pregnancy without embryonic cardiac activity, the diagnosis of early pregnancy loss is based on specific adjunctive criteria (eg, gestational sac ≥25 mm in mean diameter without a yolk sac or embryo, embryo with crown-rump length ≥7 mm). If there is uncertainty about pregnancy loss versus normal early developmental findings, then repeating the ultrasound in a week often clarifies the issue. Diagnosis of early pregnancy loss is reviewed in detail separately. (See "Pregnancy loss (miscarriage): Clinical presentations, diagnosis, and initial evaluation" and "Pregnancy loss (miscarriage): Ultrasound diagnosis".)

**Counseling after diagnosis of intrauterine pregnancy —** The individual's feelings and thoughts about the pregnancy should be addressed. A proportion of patients with positive pregnancy tests have unplanned pregnancies. If the pregnancy was not planned, parenthood may still be desired, but other options, such as adoption and pregnancy termination, should be explored in a nondirective way, as appropriate depending on the patient's reaction to receiving their test results. It is also appropriate to discuss the patient's personal circumstances, including their living situation, partner reaction to the pregnancy, intimate partner violence, and reproductive coercion [65].

Patients who elect to continue the pregnancy should receive a referral for early initiation of prenatal care and information about good health practices during early pregnancy (eg, take a multivitamin that has at least 400 mcg of folate; avoid smoking, alcohol, recreational drugs, nonprescription use of prescription drugs, and exposure to ionizing radiation; avoid consuming uncooked or undercooked meats or unpasteurized cheese; and use good practices to reduce the risk of maternal infection). (See "Prenatal care: Patient education, health promotion, and safety of commonly used drugs".)

If the patient has a medical problem or is taking a medication(s) that may be harmful in pregnancy, they should discuss this issue with an appropriate health care provider in a timely way.

**Special populations**

**Patients with an intrauterine device —** Although rare, pregnancy may occur with an intrauterine device (IUD) in place. An ultrasound should be performed to determine whether the pregnancy is intrauterine or extrauterine; most pregnancies in this setting are intrauterine, but the risk of ectopic is higher than if no IUD were present.

If the pregnancy and IUD are intrauterine, the IUD should be removed because the risk of pregnancy complications is higher if it is left in place than if it is removed, as long as the IUD string is visible. The evaluation and management of pregnancies complicated by an in situ IUD are reviewed separately. (See "Intrauterine contraception: Management of side effects and complications", section on 'Pregnancy'.)

**Patients with positive "pregnancy tests" who are not pregnant —** Rarely, a positive "pregnancy test" in a female is not due to pregnancy. In these cases, hCG may be secreted by gestational trophoblastic disease, a nontrophoblastic malignancy, the pituitary gland, or may be a false positive. Ultrasound can be useful to distinguish among these entities, as it will not identify a pregnancy and may identify the intrauterine or adnexal tumor that is the source of the hCG. A complete list of sources of hCG in these patients and their evaluation are discussed separately. (See "Human chorionic gonadotropin: Biochemistry and measurement in pregnancy and disease", section on 'Interpreting laboratory findings'.)

## WHEN TO BE CONCERNED ABOUT EARLY PREGNANCY SYMPTOMS

Knowledge of the clinical spectrum of normal early pregnancy is helpful when evaluating pregnant patients who present with one or more similar clinical symptoms but have an abnormal pregnancy or a coexistent medical or surgical disorder.

**Vaginal bleeding** — Bleeding in early pregnancy that is heavier than spotting or accompanied by any pain may represent an ectopic pregnancy ( table 5) or impending miscarriage; however, any amount of bleeding is worrisome. The approach to evaluation and management of patients with bleeding in early pregnancy is discussed in detail separately. (See "Evaluation and differential diagnosis of vaginal bleeding before 20 weeks of gestation".)

**Nausea and vomiting** — Most pregnant people experience nausea with or without vomiting, typically starting at 5 to 6 weeks of gestation, peaking at approximately 9 weeks, and usually subsiding by 16 to 20 weeks. The onset of nausea and vomiting after approximately 10 weeks should prompt an evaluation because this is after the typical gestational age expected for onset of pregnancy-related nausea and vomiting. A cause other than pregnancy should be considered if nausea and vomiting are accompanied by pain, fever, vertigo, diarrhea, headache, or abdominal distension. (See "Approach to the adult with nausea and vomiting".)

Hyperemesis gravidarum is considered the severe end of the spectrum of nausea and vomiting of pregnancy and is commonly defined as persistent vomiting accompanied by weight loss exceeding 5 percent of prepregnancy body weight and ketonuria unrelated to other causes. Alternatively, the diagnosis can be made in patients with pregnancy-related vomiting that occurs more than three times per day with weight loss greater than 3 kg or 5 percent of body weight and ketonuria. (See "Nausea and vomiting of pregnancy: Clinical findings and evaluation".)

Acute fatty liver of pregnancy, preeclampsia with severe features, and HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) are potentially life-threatening pregnancy-related disorders that can present with nausea and vomiting, but the onset of these disorders is almost always after 20 weeks of gestation. (See "Acute fatty liver of pregnancy" and "Preeclampsia: Clinical features and diagnosis" and "HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets)".)

**Urinary frequency** — Cystitis or an upper urinary tract infection should be suspected if pregnancy-related urinary frequency is accompanied by dysuria, hematuria, pyuria, fever, or flank pain. (See "Maternal adaptations to pregnancy: Renal and urinary tract physiology" and "Urinary tract infections and asymptomatic bacteriuria in pregnancy".)

**Dyspnea** — Pregnancy-related dyspnea is usually mild, of gradual onset, and not associated with other pulmonary signs or symptoms (eg, cough, wheezing, pleurisy, hemoptysis, or rales) or systemic findings (eg, fever or increase in basal heart rate by more than 15 to 20 beats/minute). If dyspnea occurs acutely or is associated with any of these symptoms, then the patient should be evaluated for pulmonary embolism or other cardiopulmonary disease (eg, pneumonia, asthma, heart failure from cardiomyopathy). (See "Maternal adaptations to pregnancy: Dyspnea and other physiologic respiratory changes" and "Approach to the pregnant patient with a respiratory infection" and "Pulmonary embolism in pregnancy: Clinical presentation and diagnosis".)

**Lightheadedness** — Pregnancy-related lightheadedness typically occurs when the individual has been standing, especially in a warm environment. It should resolve when they lie on their left side. Lightheadedness is of concern when associated with an abnormal maternal heart rate/rhythm or signs suggestive of a seizure and when it does not resolve in the lateral or head-down position. (See "Maternal adaptations to pregnancy: Cardiovascular and hemodynamic changes".)

**Abdominopelvic pain**

- Round ligament pain – The round ligaments begin near the uterine cornua, pass through the abdominal inguinal ring and along the inguinal canal, and end in the labia majora. Pain in the location of the round ligaments has been termed "round ligament pain"; it is common and a diagnosis of exclusion. The pain is typically on the right side of the abdomen/pelvis and often occurs upon waking, suddenly rolling over in bed, or other vigorous activity. The pain is believed to be caused by irritation of nearby nerve fibers or spasm of the ligament; rarely, it may be due to varicosities, myomas, or endometriosis associated with the ligament. A change in position may alleviate the pain, but no treatment is necessary, as the pain is usually mild and self-limited.

- Adnexal disorders – Adnexal disease (eg, ectopic pregnancy, ruptured ovarian cyst, ovarian torsion) should be excluded when the pain is moderate or severe, persistent or progressive, or accompanied by vaginal bleeding or peritoneal signs. (See "Ectopic pregnancy: Clinical manifestations and diagnosis" and "Adnexal mass: Evaluation and management in pregnancy".)

- Impending pregnancy loss – Midline pelvic pain and vaginal bleeding are the cardinal signs of impending or ongoing spontaneous abortion (see "Pregnancy loss (miscarriage): Terminology, risk factors, and etiology").

  Later in pregnancy (after 20 weeks of gestation), preterm labor and placental abruption should be excluded in patients with these symptoms. (See "Preterm labor: Clinical

findings, diagnostic evaluation, and initial treatment" and "Acute placental abruption: Pathophysiology, clinical features, diagnosis, and consequences".)

- Gastroesophageal reflux – Epigastric pain may be caused by gastroesophageal reflux (gastroesophageal reflux disease or heartburn), which is reported by 40 to 85 percent of pregnant people. Most studies report an increasing prevalence of symptoms from the first to the third trimester. Differential diagnosis and treatment are reviewed separately. (See "Medical management of gastroesophageal reflux disease in adults", section on 'Pregnancy and lactation'.)

  Epigastric and/or right upper quadrant pain in pregnant people can also be symptoms of preeclampsia with severe features, HELLP syndrome, or acute fatty liver of pregnancy, but the onset of these disorders is almost always after 20 weeks of gestation. (See "Acute fatty liver of pregnancy" and "Preeclampsia: Clinical features and diagnosis" and "HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets)".)

- Appendicitis – Right lower-quadrant pain is a common symptom of appendicitis, which should be excluded. Although the location of the appendix migrates a few centimeters cephalad as the uterus enlarges, the most common symptom of appendicitis (ie, right lower-quadrant pain) occurs close to McBurney's point in the majority of pregnant people, regardless of the trimester of pregnancy. (See "Acute appendicitis in pregnancy".)

**Fatigue** — Pregnancy-related fatigue has been attributed to the physiologic changes associated with pregnancy. It is most common in the first trimester, usually abates in the second trimester, and recurs to some degree in the third trimester.

In nonpregnant adults, fatigue is a common nonspecific symptom with a broad range of etiologies including acute and chronic medical disorders (eg, sleep disorders), psychological conditions (eg, depression, anxiety), medication toxicity, and substance use; any of these conditions can occur in pregnant people as well. Fatigue is of potential medical concern when associated with other signs and symptoms ( table 6). (See "Approach to the adult patient with fatigue".)

**Poor sleep** — Pregnant people experience poor sleep quality, insufficient nighttime sleep, and significant daytime sleepiness throughout pregnancy [66,67]. This is due, at least in part, to nocturia, difficulty finding a comfortable sleep position, and restless legs syndrome. (See "Restless legs syndrome during pregnancy and lactation".)

Poor sleep quality is of most concern when related to obstructive sleep apnea (OSA). Older age, higher body mass index, and frequent snoring (self-reported snoring ≥3 days per week)

is predictive of prevalent and incident sleep-disordered breathing. In addition to the usual consequences of OSA, two potential effects in pregnancy include increased risks for developing preeclampsia and gestational diabetes. There are no clear adverse fetal effects, apart from sequelae from these pregnancy complications. (See "Obstructive sleep apnea in pregnancy".)

**Back pain** — Low back pain is a common problem among pregnant people. In most cases, it is due to mechanical factors resulting from altered posture, muscle weakness, joint laxity, and/or vertebral facet joint irritation. Risk factors include preexisting back pain, back pain in a previous pregnancy, multiparity, and high body mass index [68]. (See "Maternal adaptations to pregnancy: Musculoskeletal changes and pain".)

Patients with the following symptoms warrant referral to a primary care physician, orthopedic surgeon, or neurologist:

- Severe pain that interferes with function, particularly nonpositional persistent back pain at night
- Increased pain with cough, sneezing, and Valsalva
- Neurologic deficits on examination
- At high risk of infection or compression fracture
- Systemic symptoms such as fever, chills, or weight loss

The vast majority of patients do **not** require imaging. The general approach to imaging in nonpregnant individuals with acute back pain is shown in the algorithm ( algorithm 1). When an imaging study is indicated, magnetic resonance imaging (MRI) is by far the most commonly used modality [69,70] as there are no reported adverse maternal or fetal effects from MRI during pregnancy. (See "Diagnostic imaging in pregnant and lactating patients".)

Serious causes of low back pain and risk assessment of patients with low back pain are presented in detail separately. (See "Evaluation of low back pain in adults", section on 'Serious etiologies' and "Evaluation of low back pain in adults", section on 'Risk assessment for acute back pain'.)

**Chest pain** — Chest pain not due to gastrointestinal reflux is not a normal finding in pregnancy. The evaluation of pregnant people with chest pain is the same as in nonpregnant females of similar age. (See "Outpatient evaluation of the adult with chest pain".)

**Pseudocyesis** — Pseudocyesis and delusion of pregnancy are rare psychiatric diagnoses applied to people with negative pregnancy tests who believe they are pregnant. These patients may have signs and symptoms that mimic those of actual pregnancy and can be quite convincing [71]. The signs of true pregnancy on physical examination are identification

of a fetal heart rate that is distinguishable from the maternal heart rate and palpation of fetal parts. (See "Pseudocyesis".)

**Neuropathy —** Carpal tunnel syndrome is the most common neuropathy in pregnancy. Symptoms tend to occur during the third trimester but can occur at any time. Corticosteroid injection or surgery to release the flexor retinaculum is rarely indicated during pregnancy since the disease has a better prognosis than idiopathic carpal tunnel syndrome and often resolves postpartum. (See "Neurologic disorders complicating pregnancy", section on 'Neuropathy'.)

**Headache —** Headache is common in reproductive-age females. The frequency and clinical manifestations of tension or cluster headaches are not altered during pregnancy whereas migraines may occur less frequently. The evaluation of headache in pregnancy is the same as that in nonpregnant females except preeclampsia with severe features must be excluded (or diagnosed) in all patients over 20 weeks of gestation. Management, including the choice and safety of drug therapy, depends on the type of headache and is reviewed separately. (See "Headache during pregnancy and postpartum".)

## SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: General prenatal care".)

## SUMMARY AND RECOMMENDATIONS

- **Signs and symptoms –** The most common signs and symptoms of early pregnancy are amenorrhea, nausea/vomiting, breast tenderness, urinary frequency, and fatigue ( table 4). (See 'Clinical manifestations of early pregnancy' above.)
- **Diagnosis –** The diagnosis of early pregnancy is based primarily on detecting human chorionic gonadotropin (hCG) in blood or urine. Identification of pregnancy by ultrasound examination or identification of fetal cardiac activity by Doppler ultrasound are other methods, but sensitivity depends on the gestational age. Transvaginal ultrasound examination can first visualize a gestational sac (without a fetal pole) at 4.5 to 5.0 weeks of gestation ( table 7). Fetal cardiac activity can usually be detected by a handheld Doppler device by 10 to 12 weeks of gestation. (See 'Diagnosis' above and 'Ultrasound examination' above.)
    - **Serum pregnancy tests –** A serum pregnancy test is more sensitive than a urine pregnancy test in early pregnancy (ie, just before or after a missed menstrual

period). (See 'Serum pregnancy test' above.)

- **Urine pregnancy tests** – Although the urine pregnancy test is less sensitive than the serum test, almost all pregnant people will have a positive urine pregnancy test one week after the first day of a missed menstrual period. (See 'Urine pregnancy test' above.)

- **Home pregnancy tests** – The accuracy of home pregnancy tests is affected by the sensitivity of the specific test kit, as well as the user's technique and interpretation. On the first day after a missed period, as many as 46 percent of pregnant people will have a negative test. Positive results on a home-based test should be confirmed by a serum or urine hCG test performed by a clinician or by another definitive test (eg, Doppler confirmation of fetal cardiac activity, sonographic visualization of the pregnancy). (See 'Home pregnancy test' above.)

- **Determining pregnancy location** – Because 98 percent of pregnancies are intrauterine, the pregnancy is generally assumed to be intrauterine **unless** the patient has one or more of the following:

  - Adnexal pain
  - Vaginal spotting/bleeding
  - Risk factors for an extrauterine pregnancy ( table 5)

  The evaluation for intrauterine pregnancy versus ectopic pregnancy in a patient with a pregnancy of unknown location is discussed in detail separately. (See 'Determining pregnancy location' above and "Approach to the patient with pregnancy of unknown location".)

- **Differential diagnosis of common pregnancy signs and symptoms** – Knowledge of the clinical spectrum of normal pregnancy signs and symptoms is helpful when evaluating females who present with one or more similar clinical findings but have an abnormal pregnancy or coexistent medical or surgical disorder. (See 'When to be concerned about early pregnancy symptoms' above.)



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Topic 440 Version 66.0

## GRAPHICS

### Percentage of women experiencing unintended pregnancy during the first year of contraceptive use (typical and perfect use) and the percentage continuing use at the end of the first year: United States

| Method | Percent of women experiencing an unintended pregnancy within the first year of use (%) | | Percent of women continuing use at one year (%)[Δ] |
|---|---|---|---|
| | Typical use* | Perfect use[¶] | |
| No method[◇] | 85 | 85 | |
| Spermicides[§] | 21 | 16 | 42 |
| Internal condom[¥] | 21 | 5 | 41 |
| Withdrawal | 20 | 4 | 46 |
| Diaphragm[‡] | 17 | 16 | 57 |
| Sponge | 17 | 12 | 36 |
| Parous women | 27 | 20 | |
| Nulliparous women | 14 | 9 | |
| Fertility awareness-based methods[†] | 15 | | 47 |
| Ovulation method[†] | 23 | 3 | |
| TwoDay method[†] | 14 | 4 | |
| Standard Days method[†] | 12 | 5 | |
| Natural Cycles[†] | 8 | 1 | |
| Symptothermal method[†] | 2 | 0.4 | |
| External condom[¥] | 13 | 2 | 43 |
| Combined and progestin-only pills | 7 | 0.3 | 67 |
| Evra patch | 7 | 0.3 | 67 |
| NuvaRing | 7 | 0.3 | 67 |
| Depo-Provera | 4 | 0.2 | 56 |
| Intrauterine contraceptives** | | | |
| ParaGard (copper T) | 0.8 | 0.6 | 78 |
| Mirena (52 mg LNG) | 0.7 | 0.5 | 80 |
| Skyla (13.5 mg LNG) | 0.4 | 0.3 | |
| Kyleena (19.5 mg LNG) | 0.2 | 0.2 | |

| | | | |
|---|---|---|---|
| Liletta (52 mg LNG) | 0.1 | 0.1 | |
| Nexplanon | 0.1 | 0.1 | 89 |
| Tubal occlusion | 0.5 | 0.5 | 100 |
| Vasectomy | 0.15 | 0.1 | 100 |
| **Emergency contraceptives:** Use of emergency contraceptive pills or placement of a copper intrauterine contraceptive after unprotected intercourse substantially reduces the risk of pregnancy. | | | |
| **Lactational amenorrhea method:** LAM is a highly effective, **temporary** method of contraception.[¶¶] | | | |

Estimates of the probability of pregnancy during the first year of typical use for fertility awareness-based methods, withdrawal, the external condom, the pill, and Depo-Provera are taken from the 2006 to 2010 National Survey of Family Growth (NSFG) corrected for under-reporting of abortion.

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LNG: levonorgestrel; LAM: lactational amenorrhea method; FABM: fertility awareness-based methods; NSFG: National Survey of Family Growth; LH: luteinizing hormone.

* Among typical couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any reason other than pregnancy. Data from United States populations.

¶ Among couples who initiate use of a method (not necessarily for the first time) and who use it perfectly (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

Δ Among couples attempting to avoid pregnancy, the percentage who continue to use a method for 1 year.

◇ This estimate represents the percentage who would become pregnant within 1 year among women now relying on reversible methods of contraception if they abandoned contraception altogether.

§ 150 mg gel, 100 mg gel, 100 mg suppository, 100 mg film.

¥ Without spermicides.

‡ With spermicidal cream or jelly.

† Approximately 80% of segments of FABM use in the 2006 to 2010 NSFG were reported as calendar rhythm. Specific FABM methods are too uncommonly used in the United States to permit calculation of typical use failure rates for each using NSFG data; rates provided for individual methods are derived from clinical studies. The Ovulation and TwoDay methods are based on evaluation of cervical mucus. The Standard Days method avoids intercourse on cycle days 8 through 19. Natural Cycles is a fertility app that requires user input of basal body temperature (BBT) recordings and dates of menstruation and optional LH urinary test results. The Symptothermal method is a double-check method based on evaluation of cervical mucus to determine the first fertile day and evaluation of cervical mucus and temperature to determine the last fertile day.

** All of these estimates are low, below 1%, and we caution readers not to put any emphasis on the differences among these very small probabilities.

¶¶ However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breastfeeds is reduced, bottle feeds are introduced, or the baby reaches 6 months of age.

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Graphic 120134 Version 6.0

## Pregnancy testing

| | Urine pregnancy test | Serum pregnancy test |
|---|---|---|
| **Minimum hCG level for a positive test** | Qualitative test: 20 to 50 milli-int. units/mL, depending on test | Qualitative test: 5 to 10 milli-int. units/mL, depending on test<br>Quantitative test: 1 to 2 milli-int. units/mL for an ultrasensitive test |
| **Causes of a false-negative test** | 1. Performed too soon after conception; hCG concentration is below threshold for a positive test<br>2. The hCG isoform measured is different from the hCG isoform in the sample (pertains mostly to urine tests)<br>3. Hook effect due to extremely high hCG concentration (>500,000 milli-int. units/mL, these levels are most commonly seen in gestational trophoblastic neoplasia) | |
| **Causes of a false-positive test** | 1. Operator error in performing or interpreting the test, particularly with home pregnancy tests.<br>2. Chemical pregnancy (ie, recent pregnancy loss very soon after implantation).<br>3. Exogenous hCG administered as part of infertility treatment or for athletic performance. Exogenous hCG should be cleared by two weeks post-injection.<br>4. HCG secretion from a tumor.<br>5. Pituitary hCG secretion, typically in perimenopausal women.<br>6. Interference with the assay by anti-animal antibodies, anti-hCG antibodies, or other substances (eg, high doses of biotin serum test positive but urine test is usually negative).<br>7. Familial hCG syndrome (rare genetic condition) | |

hCG: human chorionic gonadotropin.

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Graphic 88953 Version 7.0

## Reference intervals in pregnancy

| | Nonpregnant females* | First trimester | Second trimester | Third trimester | Re |
|---|---|---|---|---|---|
| **Hematology** | | | | | |
| Erythropoietin[¶] (units/L) | 4 to 27 | 12 to 25 | 8 to 67 | 14 to 222 | 1-3 |
| Ferritin[¶] (ng/mL) | 10 to 150[Δ] | 6 to 130 | 2 to 230 | 0 to 116 | 1-8 |
| Folate, red blood cell (ng/mL) | 150 to 450 | 137 to 589 | 94 to 828 | 109 to 663 | 6, 9 |
| Folate, serum (ng/mL) | 5.4 to 18.0 | 2.6 to 15.0 | 0.8 to 24.0 | 1.4 to 20.7 | 1, 6 |
| Haptoglobin (mg/mL) | 25 to 250 | 130±43 | 115±50 | 135±65 | 91 |
| Hemoglobin[¶] (g/dL) | 12 to 15.8[Δ] | 11.6 to 13.9 | 9.7 to 14.8 | 9.5 to 15.0 | 2, 3 |
| Hematocrit[¶] (%) | 35.4 to 44.4 | 31.0 to 41.0 | 30.0 to 39.0 | 28.0 to 40.0 | 1, 2 15 |
| Iron, total binding capacity[¶] (mcg/dL) | 251 to 406 | 278 to 403 | Not reported | 359 to 609 | 7 |
| Iron, serum[¶] (mcg/dL) | 41 to 141 | 72 to 143 | 44 to 178 | 30 to 193 | 2, 7 |
| Mean corpuscular hemoglobin (pg/cell) | 27 to 32 | 30 to 32 | 30 to 33 | 29 to 32 | 5 |
| Mean corpuscular volume ($\times m^3$) | 79 to 93 | 81 to 96 | 82 to 97 | 81 to 99 | 103 |
| Platelet ($\times 10^9$/L) | 165 to 415 | 174 to 391 | 155 to 409 | 146 to 429 | 5, 6 17 |
| Mean platelet volume ($mcm^3$) | 6.4 to 11.0 | 7.7 to 10.3 | 7.8 to 10.2 | 8.2 to 10.4 | 5 |
| Red blood cell count ($\times 10^6/mm^3$) | 4.00 to 5.20[Δ] | 3.42 to 4.55 | 2.81 to 4.49 | 2.71 to 4.43 | 5, 6 |
| Red cell distribution width (%) | <14.5 | 12.5 to 14.1 | 13.4 to 13.6 | 12.7 to 15.3 | 5 |
| White blood cell count ($\times 10^3/mm^3$) | 3.5 to 9.1 | 5.7 to 13.6 | 5.6 to 14.8 | 5.9 to 16.9 | 5, 6 18 |
| Neutrophils ($\times 10^3/mm^3$) | 1.4 to 4.6 | 3.6 to 10.1 | 3.8 to 12.3 | 3.9 to 13.1 | 5, |
| Lymphocytes ($\times 10^3/mm^3$) | 0.7 to 4.6 | 1.1 to 3.6 | 0.9 to 3.9 | 1.0 to 3.6 | 5, |
| Monocytes ($\times 10^3/mm^3$) | 0.1 to 0.7 | 0.1 to 1.1 | 0.1 to 1.1 | 0.1 to 1.4 | 5, |

| | | | | | |
|---|---|---|---|---|---|
| Eosinophils ($\times 10^3/mm^3$) | 0 to 0.6 | 0 to 0.6 | 0 to 0.6 | 0 to 0.6 | 14, |
| Basophils ($\times 10^3/mm^3$) | 0 to 0.2 | 0 to 0.1 | 0 to 0.1 | 0 to 0.1 | 14, |
| Transferrin (mg/dL) | 200 to 400 | 254 to 344 | 220 to 441 | 288 to 530 | 4, 5 |
| Transferrin, saturation without iron (%) | 22 to 46¶ | Not reported | 10 to 44 | 5 to 37 | 3 |
| Transferrin, saturation with iron (%) | 22 to 46¶ | Not reported | 18 to 92 | 9 to 98 | 3 |
| Hepcidin (ng/mL) | Not reported | 4 to 97 | 6 to 36 | 1 to 43 | 98, |
| **Coagulation** | | | | | |
| Antithrombin, functional (%) | 70 to 130 | 89 to 114 | 78 to 126 | 82 to 116 | 17, |
| Factor V (%) | 50 to 150 | 75 to 95 | 72 to 96 | 60 to 88 | 25 |
| Factor VII (%) | 50 to 150 | 100 to 146 | 95 to 153 | 149 to 211 | 17 |
| Factor VIII (%) | 50 to 150 | 90 to 210 | 97 to 312 | 143 to 353 | 17, |
| Factor IX (%) | 50 to 150 | 103 to 172 | 154 to 217 | 164 to 235 | 17 |
| Factor XI (%) | 50 to 150 | 80 to 127 | 82 to 144 | 65 to 123 | 17 |
| Factor XII (%) | 50 to 150 | 78 to 124 | 90 to 151 | 129 to 194 | 17 |
| Fibrinogen (mg/dL) | 211 to 496 | 244 to 510 | 291 to 538 | 301 to 696 | 5, 23, |
| Homocysteine (mmol/L) | 4.4 to 10.8 | 3.34 to 11 | 2.0 to 26.9 | 3.2 to 21.4 | 6, 9 |
| International Normalized Ratio | 0.9 to 1.04◇ | 0.86 to 1.08 | 0.83 to 1.02 | 0.80 to 1.09 | 19, |
| Partial thromboplastin time, activated (seconds) | 26.3 to 39.4 | 23.0 to 38.9 | 22.9 to 38.1 | 22.6 to 35.0 | 5, |
| Plasminogen activator inhibitor-1 (PAI-1) antigen (pg/mL) | 17.3±5.7 | 17.7±1.9 | Not reported | 66.4±4.9 | 85 |
| Plasminogen activator inhibitor-1 (PAI-1) activity (arbitrary units) | 9.3±1.9 | 9.0±0.8 | Not reported | 31.4±3.0 | 85 |
| Prothrombin time (seconds) | 12.7 to 15.4 | 9.7 to 13.5 | 9.5 to 13.4 | 9.6 to 12.9 | 5, |
| Protein C, functional (%) | 70 to 130 | 78 to 121 | 83 to 133 | 67 to 135 | 19, |
| Protein S, total (%) | 70 to 140 | 39 to 105 | 27 to 101 | 33 to 101 | 17, |
| Protein S, free (%) | 70 to 140 | 34 to 133 | 19 to 113 | 20 to 65 | 25, |

| | | | | | |
|---|---|---|---|---|---|
| Protein S, functional activity (%) | 65 to 140 | 57 to 95 | 42 to 68 | 16 to 42 | 25 |
| Tissue plasminogen activator (ng/mL) | 1.6 to 13[§] | 1.8 to 6.0 | 2.36 to 6.6 | 3.34 to 9.20 | 17, |
| Tissue plasminogen activator inhibitor-1 (ng/mL) | 4 to 43 | 16 to 33 | 36 to 55 | 67 to 92 | 17 |
| Activated protein C resistance (APC-r) | 2.12 to 5.00 | 1.79 to 4.75 | 1.00 to 2.83 | 1.61 to 5.00 | 10 |
| D-Dimer (DDU) (ng/mL) | <500 | 200 to 900 | 200 to 1600 | 400 to 500 | 21- |
| **von Willebrand measurements** | | | | | |
| von Willebrand factor antigen (%) | 75 to 125 | 62 to 318 | 90 to 247 | 84 to 422 | 20, |
| ADAMTS-13, von Willebrand cleaving protease | 40 to 170[¥] | 40 to 160 | 22 to 135 | 38 to 105 | 20, |
| **Blood chemical constituents** | | | | | |
| Alanine aminotransferase (units/L) | 7 to 41 | 3 to 30 | 2 to 33 | 2 to 25 | 4, 5 108 |
| Albumin (g/dL) | 4.1 to 5.3[Δ] | 3.1 to 5.1 | 2.6 to 4.5 | 2.3 to 4.2 | 29- |
| Alkaline phosphatase (units/L) | 33 to 96 | 17 to 88 | 25 to 126 | 38 to 229 | 4, 5 |
| Alpha-1 antitrypsin (mg/dL) | 100 to 200 | 225 to 323 | 273 to 391 | 327 to 487 | 5 |
| Alpha-fetoprotein (ng/mL) | — | — | Approximately 130-400 | Approximately 130-590 | 93 |
| Ammonia (microM) | 31±3.2 | — | — | 27.3±1.6 | 92 |
| Amylase (units/L) | 20 to 96 | 24 to 83 | 16 to 73 | 15 to 81 | 4, 5 |
| Anion gap (mmol/L) | 7 to 16 | 13 to 17 | 12 to 16 | 12 to 16 | 5 |
| Aspartate aminotransferase (units/L) | 12 to 38 | 3 to 23 | 3 to 33 | 4 to 32 | 4, 5 108 |
| Bicarbonate (mmol/L) | 22 to 30 | 20 to 24 | 20 to 24 | 20 to 24 | 5 |
| Bilirubin, total (mg/dL) | 0.3 to 1.3 | 0.1 to 0.4 | 0.1 to 0.8 | 0.1 to 1.1 | 4, 2 |
| Bilirubin, unconjugated (mg/dL) | 0.2 to 0.9 | 0.1 to 0.5 | 0.1 to 0.4 | 0.1 to 0.5 | 5, 2 |
| Bilirubin, conjugated (mg/dL) | 0.1 to 0.4 | 0 to 0.1 | 0 to 0.1 | 0 to 0.1 | 29 |

| | | | | | |
|---|---|---|---|---|---|
| Bile acids (micromol/L) | 0.3 to 4.8‡ | 0 to 4.9 | 0 to 9.1 | 0 to 11.3 | 29, |
| CA 125 antigen (units/mL) | 7.2 to 27.0 | 2/2 to 268 | 12 to 25.1 | 16.8 to 43.8 | 86, |
| Calcium, ionized (mg/dL) | 4.5 to 5.3 | 4.5 to 5.1 | 4.4 to 5.0 | 4.4 to 5.3 | 5, 3 |
| Calcium, total (mg/dL) | 8.7 to 10.2 | 8.8 to 10.6 | 8.2 to 9.0 | 8.2 to 9.7 | 4, 5 36- |
| Ceruloplasmin (mg/dL) | 25 to 63 | 30 to 49 | 40 to 53 | 43 to 78 | 5, 3 |
| Chloride (mEq/L) | 102 to 109 | 101 to 105 | 97 to 109 | 97 to 109 | 4, 5 |
| Creatinine (mg/dL) | 0.5 to 0.9Δ | 0.4 to 0.7 | 0.4 to 0.8 | 0.4 to 0.9 | 4, 5 |
| Gamma-glutamyl transpeptidase (units/L) | 9 to 58 | 2 to 23 | 4 to 22 | 3 to 26 | 4, 5 |
| Lactate dehydrogenase (units/L) | 115 to 221 | 78 to 433 | 80 to 447 | 82 to 524 | 4, 5 |
| Lead (microg/dL) | Not reported | 6.8 to 7.7 | 5.8 to 6.6 | 6.8 to 7.8 | 11( |
| Lipase (units/L) | 3 to 43 | 21 to 76 | 26 to 100 | 41 to 112 | 33 |
| Magnesium (mg/dL) | 1.5 to 2.3 | 1.6 to 2.2 | 1.5 to 2.2 | 1.1 to 2.2 | 4, 5 36, |
| Osmolality (mOsm/kg H20) | 275 to 295 | 275 to 280 | 276 to 289 | 278 to 280 | 38, |
| Phosphate (mg/dL) | 2.5 to 4.3 | 3.1 to 4.6 | 2.5 to 4.6 | 2.8 to 4.6 | 4, 5 42 |
| Potassium (mEq/L) | 3.5 to 5.0 | 3.6 to 5.0 | 3.3 to 5.0 | 3.3 to 5.1 | 4, 5 32, |
| Prealbumin (mg/dL) | 17 to 34 | 15 to 27 | 20 to 27 | 14 to 23 | 5 |
| Protein, total (g/dL) | 6.7 to 8.6 | 6.2 to 7.6 | 5.7 to 6.9 | 5.6 to 6.7 | 5, 3 |
| Sodium (mEq/L) | 136 to 146 | 133 to 148 | 129 to 148 | 130 to 148 | 4, 5 32, |
| Urea nitrogen (mg/dL) | 7 to 20 | 7 to 12 | 3 to 13 | 3 to 11 | 4, 5 |
| Uric acid (mg/dL) | 2.5 to 5.6Δ | 2.0 to 4.2 | 2.4 to 4.9 | 3.1 to 6.3 | 4, 5 |
| **Metabolic and endocrine tests** | | | | | |
| Adiponectin (ng/dL) | Not reported | 1141 to 13,499 | 1205 to 16,035 | 1428 to 13,857 | 11 |
| Aldosterone (ng/dL) | 2 to 9 | 6 to 104 | 9 to 104 | 15 to 101 | 43, |
| Angiotensin converting enzyme (units/L) | 9 to 67 | 1 to 38 | 1 to 36 | 1 to 39 | 39, |
| Alpha-fetoprotein (ng/mL) | 0 to 8.5 | Not reported | 50 to 425 | 50 to 590 | 82, |
| Cortisol (mcg/dL) | 0 to 25 | 7 to 19 | 10 to 42 | 12 to 50 | 5, 4 |

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|---|---|---|---|---|---|
| Hemoglobin $A_{1C}$ (%) | 4 to 6 | 4 to 6 | 4 to 6 | 4 to 7 | 36, |
| Iodine (urine, microg/dL) | Not reported | 75 to 291 | 89 to 316 | Not reported | 11 |
| Leptin (pg/mL) | Not reported | 5594 to 166,097 | 1401 to 96,912 | 3997 to 189,930 | 11 |
| Parathyroid hormone (pg/mL) | 8 to 51 | 10 to 15 | 18 to 25 | 9 to 26 | 30 |
| Parathyroid hormone-related protein (pmol/L) | <1.3† | 0.7 to 0.9 | 1.8 to 2.2 | 2.5 to 2.8 | 30 |
| Renin, plasma activity (ng/mL/hour) | 0.3 to 9.0† | Not reported | 7.5 to 54.0 | 5.9 to 58.8 | 40, |
| Thyroid-stimulating hormone (milli-int. units/mL) | 0.34 to 4.25 | 0.60 to 3.40 | 0.37 to 3.60 | 0.38 to 4.04 | 4, 5 |
| [American Thyroid Association recommendation]** | | 0.1 to 2.5 | 0.2 to 3.0 | 0.3 to 3.0 | 83 |
| Thyroxine-binding globulin (mg/dL) | 1.3 to 3.0 | 1.8 to 3.2 | 2.8 to 4.0 | 2.6 to 4.2 | 5 |
| Thyroxine, free (ng/dL) | 0.8 to 1.7 | 0.8 to 1.2 | 0.6 to 1.0 | 0.5 to 0.8 | 5, 4 |
| Thyroxine, total (mcg/dL) | 5.4 to 11.7 | 6.5 to 10.1 | 7.5 to 10.3 | 6.3 to 9.7 | 5, 3 |
| Triiodothyronine, free (pg/mL) | 2.4 to 4.2 | 4.1 to 4.4 | 4.0 to 4.2 | Not reported | 49 |
| Triiodothyronine, total (ng/dL) | 77 to 135 | 97 to 149 | 117 to 169 | 123 to 162 | 5 |
| **Vitamins and minerals** | | | | | |
| Copper (mcg/dL) | 70 to 140 | 112 to 199 | 165 to 221 | 130 to 240 | 50, |
| Selenium (mcg/L) | 63 to 160 | 116 to 146 | 75 to 145 | 71 to 133 | 5, 5 |
| Vitamin A (retinol) (mcg/dL) | 20 to 100 | 32 to 47 | 35 to 44 | 29 to 42 | 5 |
| Vitamin B12 (pg/mL) | 279 to 966 | 118 to 438 | 130 to 656 | 99 to 526 | 6, 1 |
| Vitamin C (ascorbic acid) (mg/dL) | 0.4 to 1.0 | Not reported | Not reported | 0.9 to 1.3 | 52 |
| Vitamin D, 1,25-dihydroxy (pg/mL) | 25 to 45 | 20 to 65 | 72 to 160 | 60 to 119 | 30, |
| Vitamin D, 24,25-dihydroxy (ng/mL) | 0.5 to 5.0† | 1.2 to 1.8 | 1.1 to 1.5 | 0.7 to 0.9 | 53 |
| Vitamin D, 25-hydroxy (ng/mL) | 14 to 80 | 18 to 27 | 10 to 22 | 10 to 18 | 30, |

| | | | | | |
|---|---|---|---|---|---|
| Vitamin E (α-tocopherol) (mcg/mL) | 5 to 18 | 7 to 13 | 10 to 16 | 13 to 23 | 5 |
| Zinc (mcg/dL) | 75 to 120 | 57 to 88 | 51 to 80 | 50 to 77 | 5, |
| **Autoimmune and inflammatory mediators** | | | | | |
| C3 complement (mg/dL) | 83 to 177 | 62 to 98 | 73 to 103 | 77 to 111 | 5 |
| C4 complement (mg/dL) | 16 to 47 | 18 to 36 | 18 to 34 | 22 to 32 | 5 |
| C-reactive protein (mg/L) | 0.2 to 3.0 | Not reported | 0.4 to 20.3 | 0.4 to 8.1 | 54 |
| Erythrocyte sedimentation rate (mm/hour) | 0 to 20[Δ] | 4 to 57 | 7 to 47 | 13 to 70 | 55 |
| Immunoglobulin A (mg/dL) | 70 to 350 | 95 to 243 | 99 to 237 | 112 to 250 | 5 |
| Immunoglobulin G (mg/dL) | 700 to 1700 | 981 to 1267 | 813 to 1131 | 678 to 990 | 5 |
| Immunoglobulin M (mg/dL) | 50 to 300 | 78 to 232 | 74 to 218 | 85 to 269 | 5 |
| Procalcitonin (ng/mL) | Not reported | 0.03 | 0.04 | 0.05 | 11 |
| **Sex hormones** | | | | | |
| Dehydroepiandrosterone sulfate (mmol/L) | 1.3 to 6.8[†] | 2.0 to 16.5 | 0.9 to 7.8 | 0.8 to 6.5 | 56 |
| Estradiol (pg/mL) | <20 to 443[Δ,¶¶] | 188 to 2497 | 1278 to 7192 | 614 to 3460 | 56, |
| Progesterone (ng/mL) | <1 to 20[Δ] | 8 to 48 | | 99 to 342 | 56, |
| Prolactin (ng/mL) | 0 to 20 | 36 to 213 | 110 to 330 | 137 to 372 | 30, |
| Sex hormone binding globulin (nmol/L) | 18 to 114[Δ] | 39 to 131 | 214 to 717 | 216 to 724 | 56, |
| Testosterone (ng/dL) | 6 to 86[Δ] | 25.7 to 211.4 | 34.3 to 242.9 | 62.9 to 308.6 | 56 |
| 17-hydroxyprogesterone (nmol/L) | 0.6 to 10.6[Δ,†] | 5.2 to 28.5 | 5.2 to 28.5 | 15.5 to 84 | 56 |
| **Lipids** | | | | | |
| Cholesterol, total (mg/dL) | <200 | 141 to 210 | 176 to 299 | 219 to 349 | 5, |
| High-density lipoprotein cholesterol (mg/dL) | 40 to 60 | 40 to 78 | 52 to 87 | 48 to 87 | 5, |
| Low-density lipoprotein cholesterol (mg/dL) | <100 | 60 to 153 | 77 to 184 | 101 to 224 | 5, |

| | | | | | |
|---|---|---|---|---|---|
| Very-low-density lipoprotein cholesterol (mg/dL) | 6 to 40[†] | 10 to 18 | 13 to 23 | 21 to 36 | 62 |
| Triglycerides (mg/dL) | <150 | 40 to 159 | 75 to 382 | 131 to 453 | 4, 5 |
| Apolipoprotein A-I (mg/dL) | 119 to 240 | 111 to 150 | 142 to 253 | 145 to 262 | 4, 4 |
| Apolipoprotein B (mg/dL) | 52 to 163 | 58 to 81 | 66 to 188 | 85 to 238 | 4, 4 |
| **Cardiac function** | | | | | |
| Cardiac output (L/minute) | 4.8 to 6.8 | 5.6 to 9.7 | 5.5 to 9.9 | 4.8 to 8.7 | 64, 68 |
| Cardiac index (L/min/$m^2$) | 2.6 to 4.2 | 3.2 to 4.6 | 3.1 to 4.7 | 2.5 to 4.4 | 65, |
| Stroke volume (mL) | 79 to 90 | 77.5 to 107.6 | 70.3 to 107.6 | 54 to 99 | 65, |
| Stroke index (mL/$m^2$) | | 46 to 62 | 39 to 62 | 30 to 42 | 65 |
| Systemic vascular resistance (dyns/$cm^5$) | 700 to 1600 | 747 to 1485 | 692 to 1201 | 1034 to 1201 | 65, |
| **Echocardiography** | | | | | |
| Intraventricular septal dimension (cm) | 0.7 to 0.9 | 0.63 to 0.83 | 0.65 to 0.85 | 0.66 to 0.9 | 68, 90 |
| Posterior ventricular wall dimension (cm) | 0.75 to 0.9 | 0.56 to 0.8 | 0.59 to 0.9 | 0.59 to 0.9 | 68, 90 |
| Left ventricular mass (g) | 116 to 143 | 108 to 167 | 115 to 150 | 128 to 162 | 68, |
| Left ventricular mass index | 40 to 78 | 53 to 79 | 58 to 82 | 60 to 88 | 68, |
| E/A ratio | 1.4 to 1.75 | 1.6 | 1.4 | 1.3 | 68, |
| Left ventricular diastolic diameter (cm) | 4.3 to 4.8 | 4.3 to 4.6 | 4.4 to 4.9 | 5.1 | 69, |
| Left ventricular systolic diameter (cm) | 2.8 to 3.1 | 2.8 to 2.9 | 2.8 to 3.4 | 2.8 to 3.3 | 69, |
| Left vent, fractional shortening (%) | 35 to 36 | 35 to 37 | 3.5 | 35 to 36 | 69, |
| Left vent ejection fraction (%) | 60 to 73 | 61 to 75 | 61 to 63 | 60 to 73 | 69, |
| **Diastolic function** | | | | | |
| Mitral E wave (m/second) | 0.77±0.11 | 0.85±0.13 | 0.84±0.16 | 0.77±0.15 | 89, |
| Mitral A wave (m/second) | 0.46±0.1 | 0.5±0.09 | 0.5±0.1 | 0.55±0.1 | 89, |
| Isovolumic relaxation time (m/second) | 69±10 | 50±10 | 79±18 | 72±16 | 89, |

| | | | | | |
|---|---|---|---|---|---|
| **Cardiac function (blood tests)** | | | | | |
| Atrial natriuretic peptide (pg/mL) | Not reported | Not reported | 28.1 to 70.1 | Not reported | 73 |
| B-type natriuretic peptide (pg/mL) | <167 (age- and gender-specific) | 18.4 | 13.5 to 29.5 | 15.5 to 46 | 71, |
| Creatine kinase (units/L) | 39 to 238[Δ] | 27 to 83 | 25 to 75 | 13 to 101 | 5, 7 |
| Creatine kinase-MB (units/L) | <6[ΔΔ] | — | — | 1.8 to 2.4 | 74 |
| N-terminal pro-brain natriuretic peptide (pg/mL) | 50±26 | 60±45 | 60±40 | 43±34 | 94, |
| Troponin I (hs-TnI) | 0 to 1.0 | 0 to 1.0 | 0 to 1.0 | 0 to 1.0 | 10 |
| **Blood gas** | | | | | |
| pH | 7.38 to 7.42 (arterial) | 7.36 to 7.52 (venous) | 7.40 to 7.52 (venous) | 7.41 to 7.53 (venous)<br>7.39 to 7.45 (arterial) | 31, |
| $PO_2$ (mmHg) | 90 to 100 | 93 to 100 | 90 to 98 | 92 to 107 | 75, |
| $PCO_2$ (mmHg) | 38 to 42 | Not reported | Not reported | 25 to 33 | 75 |
| Bicarbonate ($HCO_3^-$) (mEq/L) | 22 to 26 | Not reported | Not reported | 16 to 22 | 75 |
| **Renal function tests** | | | | | |
| Effective renal plasma flow (mL/minute) | 492 to 696[Δ,†] | 696 to 985 | 612 to 1170 | 595 to 945 | 77, |
| Glomerular filtration rate (GFR) (mL/minute) | 106 to 132[Δ] | 131 to 166 | 135 to 170 | 117 to 182 | 77, |
| Filtration fraction (%) | 16.9 to 24.7[◇◇] | 14.7 to 21.6 | 14.3 to 21.9 | 17.1 to 25.1 | 77, |
| Osmolarity, urine (mOsm/kg) | 500 to 800 | 326 to 975 | 278 to 1066 | 238 to 1034 | 80 |
| 24-h albumin excretion (mg/24 hours) | <30 | 5 to 15 | 4 to 18 | 3 to 22 | 80, |
| 24-h calcium excretion (mmol/24 hours) | <7.5[†] | 1.6 to 5.2 | 0.3 to 6.9 | 0.8 to 4.2 | 15 |
| 24-h creatinine clearance (mL/minute) | 91 to 130 | 69 to 140 | 55 to 136 | 50 to 166 | 15, |
| 24-h creatinine excretion (mmol/24 hours) | 8.8 to 14[†] | 10.6 to 11.6 | 10.3 to 11.5 | 10.2 to 11.4 | 80 |

| | | | | | |
|---|---|---|---|---|---|
| 24-h potassium excretion (mmol/24 hours) | 25 to 100[†] | 17 to 33 | 10 to 38 | 11 to 35 | 15 |
| 24-h protein excretion (mg/24 hours) | <150 | 19 to 141 | 47 to 186 | 46 to 185 | 81 |
| 24-h sodium excretion (mmol/24 hours) | 100 to 260[†] | 53 to 215 | 34 to 213 | 37 to 149 | 15, |
| **Pulmonary function tests** | | | | | |
| Forced vital capacity (FVC) (L) | 4.00±0.51 | 3.89±0.48 | 3.92±0.48 | 4.00±0.53 | 96 |
| Forced expiratory volume in one second (FEV1) (L) | 3.20±0.41 | 3.18±0.44 | 3.16±0.39 | 3.20±0.43 | 96 |
| Peak expiratory flow (PEF) (L/second) | 7.18±1.05 | 6.71±1.19 | 6.92±1.13 | 7.19±1.10 | 96 |
| Tidal volume (L) | 0.21 to 0.48 | 0.52±0.15 | 0.54±0.15 | 0.57±0.14 | 10 |
| Minute ventilation (L) | 2.27 to 10.35 | 12.63±3.89 | 13.05±3.55 | 14.08±4.07 | 10 |

A pregnancy laboratory reference interval is an approximation of what can be expected in the overall healthy pregnant population. A value inside or outside of the interval does not necessarily indicate the presence or absence of a disorder in an individual patient.

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* Unless otherwise specified, all normal reference values are from the seventeenth edition of *Harrison's Principles of Internal Medicine*[82].

¶ Range includes references with and without iron supplementation.

Δ Normal reference range is specific range for females.

◇ Reference values are from Cerneca et al: Coagulation and fibrinolysis changes in normal pregnancy increased levels of procoagulants and reduced levels of inhibitors during pregnancy induce a hypercoagulable state, combined with a reactive fibrinolysis[19].

§ References values are from Cerneca et al and Choi et al: Tissue plasminogen activator levels change with plasma fibrinogen concentrations during pregnancy[17,19].

¥ Reference values are from Mannuci et al: Changes in health and disease of the metalloprotease that cleaves von Willebrand factor[28].

‡ Reference values are from Bacq Y et al: Liver function tests in normal pregnancy: a prospective study of 102 pregnant women and 102 matched controls[29].

† Reference values are from the fifteenth edition of *Harrison's Principles of Internal Medicine*[83].

** The American Thyroid Association recommends these TSH ranges if individual laboratories do not determine their own trimester-specific reference ranges.

¶¶ Range is for premenopausal females and varies by menstrual cycle phase.

ΔΔ Reference values are from Leiserowitz GS et al: Creatine kinase and its MB isoenzyme in the third trimester and the peripartum period[74].

◇◇ Reference values are from Dunlop W: Serial changes in renal haemodynamics during normal human pregnancy[77].

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*Updated with information from: Abbassi-Ghanavati M, Greer LG. Reference Table of Normal Laboratory Values in Uncomplicated Pregnancies. In: Cunningham FG, Leveno KJ, Bloom S, Dashe JD, Hoffman BL, Casey BM, Spong CY. Williams Obstetrics, 25th Edition. New York: McGraw-Hill, 2018.*

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Graphic 81137 Version 51.0

## Yolk sac

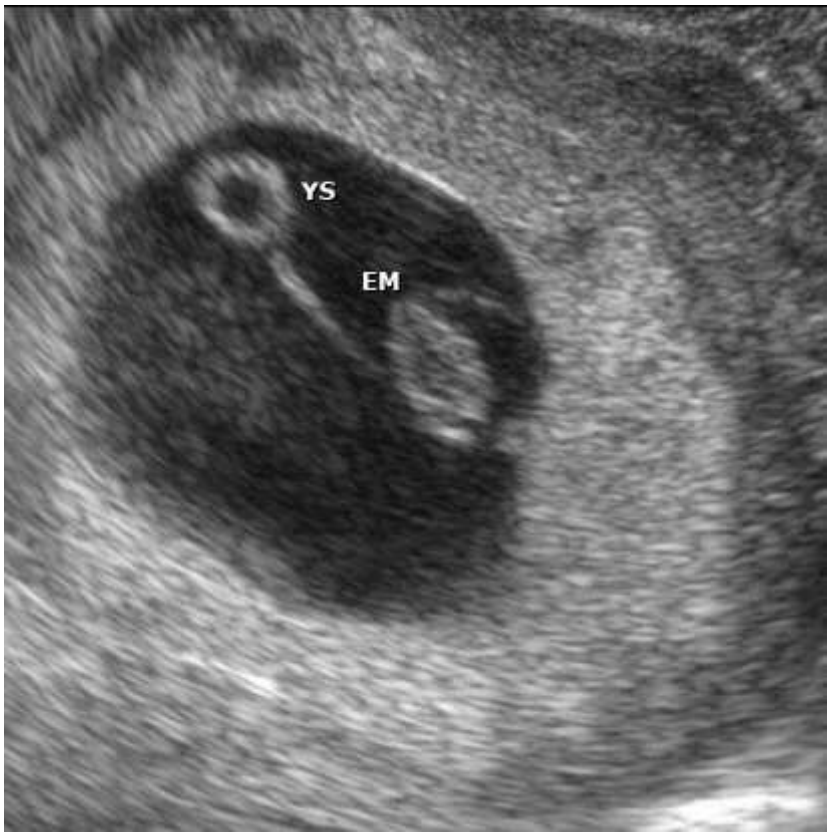


Image of an early gestational sac containing a yolk sac and early embryo. The yolk sac is the circular hyperechoic structure adjacent to the embryo.

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YS: yolk sac; EM: embryo.

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*Courtesy of Thomas Shipp, MD.*

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Graphic 65928 Version 5.0

## Measurement of embryo in gestational sac

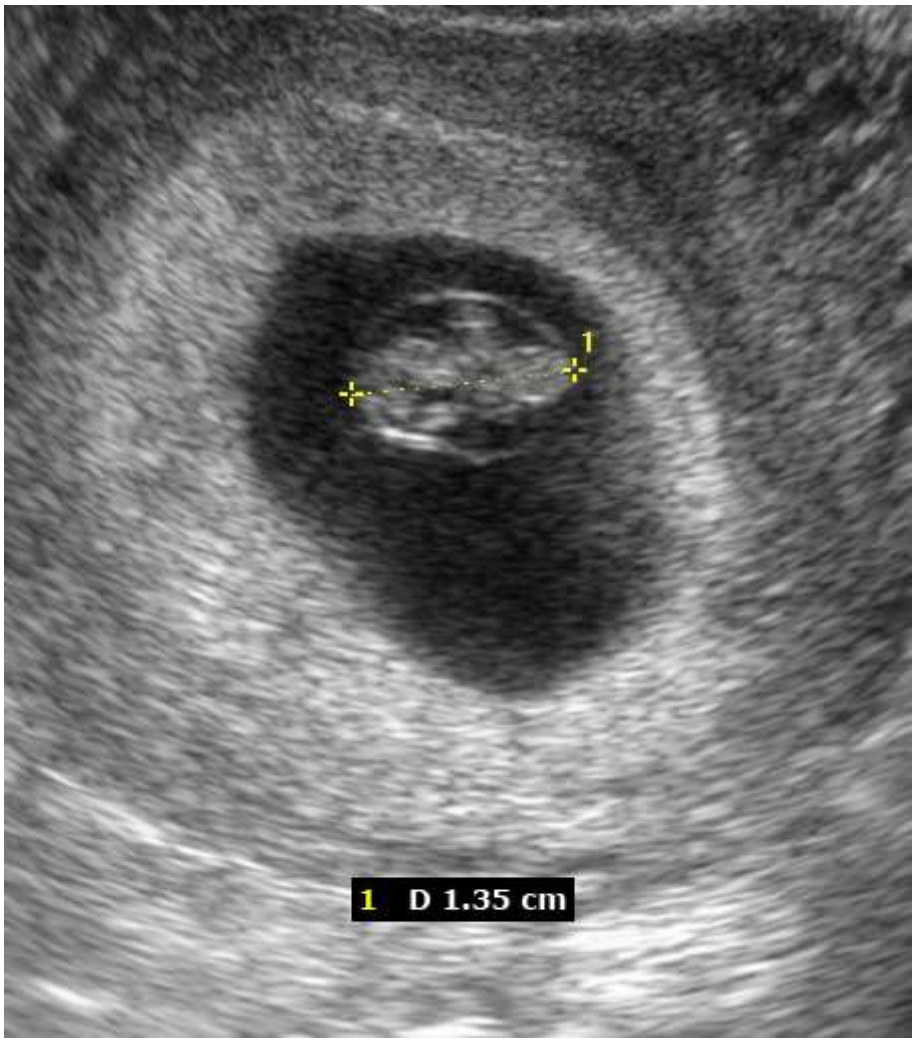


Image of an early gestational sac demonstrating the early embryo. Calipers are placed at both ends of the embryo measuring the longest length from the "crown to the rump," giving the crown-rump length. This measurement is used for dating the pregnancy. Surrounding the embryo is the developing amnion as shown by the hyperechoic circular line. Note how the amnion is the approximate size of CRL at this gestational age of about 7.5 weeks.

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*Courtesy of Thomas Shipp, MD.*

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Graphic 76430 Version 7.0

## Summary of studies reporting likelihood ratios for prediction of pregnancy

| History | Positive likelihood ratio (95% confidence interval) |
|---|---|
| Delayed menses | 2.06 (95% CI 1.65-2.57) |
| | 1.04 (95% CI 0.38-2.87) |
| | 1.13 (95% CI 1.05-2.92) |
| | 1.56 (95% CI 1.4-1.74) |
| No contraception | 1.31 (95% CI 1.14-1.5) |
| | 1.53 (95% CI 1.06-2.18) |
| Patient suspects that she is pregnant | 1.6 (95% CI 1.39-1.85) |
| | 3.15 (95% CI 2.37-4.2) |
| | 1.6 (95% CI 1.39-1.85) |
| | 2.11 (95% CI 1.97-2.27) |
| Nausea and vomiting | 2.7 (95% CI 2.19-3.33) |
| Any pregnancy symptoms (defined as nausea and vomiting, breast tenderness and fullness, urinary frequency, or fatigue) | 2.43 (95% CI 1.71-3.44) |
| Characteristic breast changes on physical examination* | 2.71 (95% CI 2.3-3.2) |
| Palpable fundus on physical examination | 2.77 (95% CI 1.7-4.51) |
| Chadwick sign present¶ | 3.17 (95% CI 2.22-4.51) |
| Uterine artery pulsations present | 10.98 (95% CI 5.63-21.4) |

* Breasts become fuller and more tender. The areola darkens and the veins under the breast skin become more visible.

¶ Bluish discoloration of the cervix and vagina resulting from increased blood flow during pregnancy.

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## Risk factors for ectopic pregnancy compared with pregnant controls

| Degree of risk | Risk factors | Odds ratio |
|---|---|---|
| High | Previous ectopic pregnancy | 2.7 to 8.3 |
| | Previous tubal surgery | 2.1 to 21 |
| | Tubal pathology | 3.5 to 25 |
| | Sterilization | 5.2 to 19 |
| | IUD | |
| | ▪ Past use | 1.7 |
| | ▪ Current use | 4.2 to 16.4 |
| | ▪ Levonorgestrel IUD | 4.9* |
| | In vitro fertilization in current pregnancy | 4 to 9.3 |
| Moderate | Current use of estrogen/progestin oral contraceptives | 1.7 to 4.5 |
| | Previous sexually transmitted infections (gonorrhea, chlamydia) | 2.8 to 3.7 |
| | Previous pelvic inflammatory disease | 2.5 to 3.4 |
| | In utero DES exposure | 3.7 |
| | Smoking | |
| | ▪ Past smoker | 1.5 to 2.5 |
| | ▪ Current smoker | 1.7 to 3.9 |
| | Previous pelvic/abdominal surgery | 4 |
| | Previous spontaneous abortion | 3 |
| Low | Previous medically induced abortion | 2.8 |
| | Infertility | 2.1 to 2.7 |
| | Age ≥40 years | 2.9 |
| | Vaginal douching | 1.1 to 3.1 |
| | Age at first intercourse <18 years | 1.6 |

| | | |
|---|---|---|
| | Previous appendectomy | 1.6 |

IUD: intrauterine device; DES: diethylstilbestrol.

* Rates of ectopic pregnancy may be higher among those using the 13.5 mg compared with the 52 mg levonorgestrel IUD. This is discussed in related UpToDate content.

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*Data from:*


- *Clayton HB, Schieve LA, Peterson HB, et al. Ectopic pregnancy risk with assisted reproductive technology procedures. Obstet Gynecol 2006; 107:595.*
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Graphic 82282 Version 10.0

## Causes of subacute and chronic fatigue

| Condition | Symptoms | Physical findings | Supportive diagnostic studies |
|---|---|---|---|
| **Cardiopulmonary** | | | |
| Congestive heart failure | Dyspnea on exertion, orthopnea, leg swelling | S3 gallop, inspiratory rales, elevated jugular venous distension, peripheral edema | Chest radiograph, echocardiogram |
| Chronic obstructive pulmonary disease | Dyspnea, chronic cough, sputum production | Evidence of hyperinflation, wheezing, rales | Chest radiograph |
| Sleep apnea | Snoring, interrupted breathing during sleep | Obesity, hypertension | Sleep study |
| **Endocrinologic/metabolic** | | | |
| Hypothyroidism | Cold intolerance, weight gain, constipation, dry skin | Bradycardia, goiter, slow deep tendon reflex relaxation phase | Thyroid function tests |
| Hyperthyroidism | Heat intolerance, weight loss, diarrhea, moist skin | Tachycardia, goiter, ophthalmopathy | Thyroid function tests |
| Chronic renal disease | Nausea/vomiting, mental status changes, decreased urine | Hypertension, peripheral edema | Renal function tests/ serum electrolytes |
| Chronic hepatic disease | Abdominal distention, gastrointestinal bleeding | Jaundice, palmar erythema, gynecomastia, splenomegaly, evidence of ascites | Hepatic function tests |
| Adrenal insufficiency | Weight loss, salt craving, gastrointestinal complaints | Hypotension, hyperpigmentation, vitiligo | Morning cortisol/ACTH, ACTH stimulation test |
| Electrolyte abnormalities | | | |
| Hyponatremia | Nausea, malaise, cognitive dysfunction | Generally normal exam | Serum sodium level |
| Hypercalcemia | Anorexia, polydipsia/polyuria, nausea | Generally normal exam | Serum calcium/albumin levels |

| | | | |
|---|---|---|---|
| **Hematologic/neoplastic** | | | |
| Anemia | Dizziness, weakness, palpitations, dyspnea | Tachycardia, pallor | Complete blood count |
| Occult malignancy | Weight loss, localized symptoms may be present depending upon type | Variable | Variable depending upon type |
| **Infectious diseases** | | | |
| Mononucleosis syndrome | Fever, sore throat, tender lymph nodes | Fever, exudate pharyngitis, tender cervical adenopathy | Complete blood/differential count, monospot |
| Viral hepatitis | Fever, nausea/vomiting, abdominal discomfort | Fever, jaundice, tender hepatomegaly | Hepatic function tests, viral hepatitis serologies |
| HIV infection | Weight loss, variable localized complaints | Variable physical findings | HIV serology |
| Subacute bacterial endocarditis | Fever/chills, night sweats, myalgias | Fever, new (regurgitant) murmur, peripheral manifestations | Blood cultures, echocardiogram |
| Tuberculosis | Fever/chills, night sweats, fatigue, weight loss | Cough, chest pain, dyspnea, hemoptysis | PPD/gamma-interferon assay, chest radiograph |
| **Rheumatologic** | | | |
| Fibromyalgia | Chronic diffuse muscle pain | Multiple "tender points" on palpation | None |
| Polymyalgia rheumatica | Aching/morning stiffness of shoulders, neck, and hips | Decreased range of motion of shoulders, neck, and hips | Erythrocyte sedimentation rate |
| **Psychological** | | | |
| Depression | Sad mood, anhedonia, altered sleep, cognitive dysfunction | Generally normal exam | Screening test (eg, PHQ-2, PHQ-9) |
| Anxiety disorder | Generalized nervousness, panic attacks, phobias | Tachycardia, muscle tension | Screening test (eg, GAD-7) |
| Somatization disorder | Multiple chronic constitutional and localized complaints | Generally normal exam | Screening test (eg, SSS-8) |
| **Medication toxicity*** | | | |

| | | | |
|---|---|---|---|
| | Variable | Generally normal exam | None |
| **Substance use**¶ | | | |
| | Variable | Generally normal exam | None |

ACTH: adrenocorticotropic hormone; HIV: human immunodeficiency virus; PPD: purified protein derivative; PHQ-2: Patient Health Questionnaire-2; GAD-7: Generalized Anxiety Disorder-7; SSS-8: Somatic Symptom Scale-8.

* Benzodiazepines, antidepressants, muscle relaxants, first-generation antihistamines, beta-blockers, opioids, GABA analogues.

¶ Alcohol, marijuana, opioids, cocaine/other stimulants.

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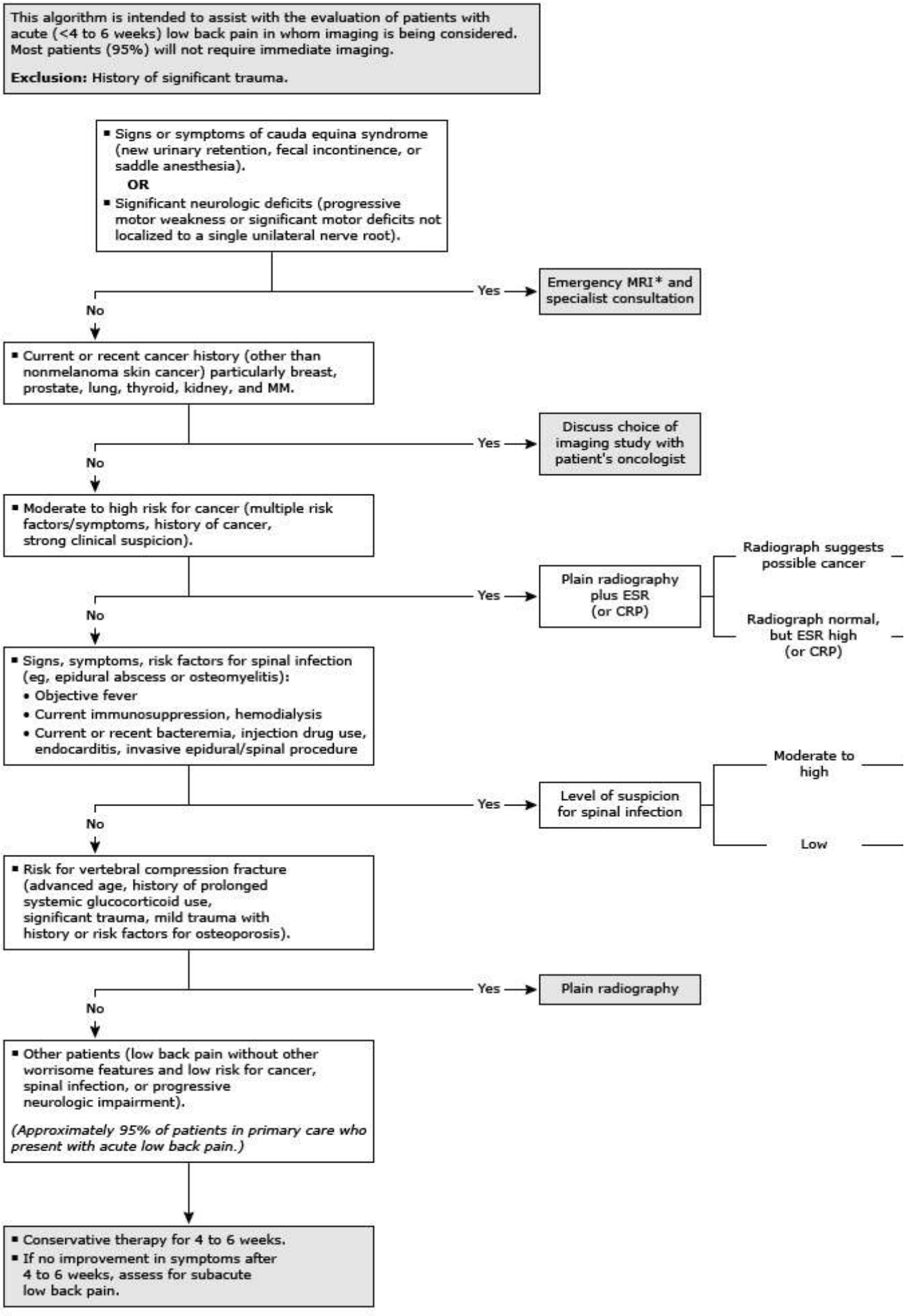
Graphic 116315 Version 3.0

# Acute low back pain: Considerations for imaging




MRI: magnetic resonance imaging; MM: multiple myeloma; ESR: erythrocyte sedimentation rate; CRP: C-

* Lumbar spine MRI without contrast is usually appropriate. If there is concern for cancer or infection or without and with contrast is recommended. CT with contrast is the alternative exam if MRI is contraindic

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Graphic 103713 Version 8.0

## Timing of first appearance of gestational landmarks on transvaginal ultrasound examination

| Landmark | First appearance on transvaginal ultrasound examination |
|---|---|
| Gestational sac | 4.5 to 5 weeks |
| Yolk sac | 5 weeks |
| Cardiac activity | 5.5 to 6 weeks |
| Measurable crown-rump length | 6 weeks |

The yolk sac is visible when the mean gestational sac diameter (MSD) is 8 mm and fetal cardiac activity can be observed when MSD is 16 mm. For transabdominal sonograms, the corresponding MSDs are larger than 20 and 25 mm, respectively. MSD = (length + height + width of the gestational sac)/3. In addition, MSD(mm)+30 = gestational age(days).

## Contributor Disclosures

**Lori A Bastian, MD, MPH** No relevant financial relationship(s) with ineligible companies to disclose. **Haywood L Brown, MD** Other Financial Interest: Merck [Mother's Global Health Advisory Board]. All of the relevant financial relationships listed have been mitigated. **Charles J Lockwood, MD, MHCM** No relevant financial relationship(s) with ineligible companies to disclose. **Vanessa A Barss, MD, FACOG** No relevant financial relationship(s) with ineligible companies to disclose.

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