Prenatal care: Patient education, health promotion, and safety of commonly used drugs

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INTRODUCTION — Prenatal care in the first few prenatal visits involves a substantial amount of patient education and health promotion. This topic will discuss routine patient education and health promotion in early pregnancy and use of common medications across pregnancy. Other important aspects of prenatal care are reviewed separately. (See "Prenatal care: Initial assessment" and "Prenatal care: Second and third trimesters".)

PATIENT EDUCATION AND HEALTH PROMOTION

Practice issues — Women should be informed about the following:

- When to call the provider (eg, vaginal bleeding or change in vaginal discharge, leakage of fluid from the vagina, fever, pain, vomiting, acute shortness of breath, calf or leg pain, headache, visual changes, dysuria, pruritus, uterine contractions, crampy abdominal pain, decreased fetal activity [after perception of fetal activity has become established], fainting or dizziness, or personal concern about a change in health status).
- How to reach the provider after business hours, coverage arrangements, and the role of various office personnel.
- The hospital where delivery will occur.
- Confidentiality issues (eg, information left on phone answering machines, use of electronic mail, and discussions with family members). There should be an explanation of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and how it affects the patient (information is available at www.hhs.gov/ocr/hipaa/).

Diet, supplements, and weight gain

Vitamins and minerals — A standard prenatal multivitamin with iron and folic acid satisfies the daily vitamin and mineral requirements of most pregnant women. Although prenatal multivitamin use has not been proven to improve maternal and neonatal outcomes in high income countries like the United Kingdom, where women are typically well-nourished and food is vitamin-fortified, in the absence of a careful evaluation of a pregnant woman's nutritional status or consultation with a nutritionist, we believe it is prudent to recommend one Micronutrient supplementation is discussed in more detail separately. (See "Nutrition in pregnancy", section on 'Micronutrients'.)

The multivitamin should contain iron 15 to 30 mg to prevent iron deficiency anemia; the Centers for Disease Control and Prevention (CDC) recommends 30 mg/day to achieve the 30 mg Recommended Daily Allowance for pregnant women [1]. However, if daily intake of a multivitamin containing iron is poorly tolerated, a vitamin without iron and intermittent iron supplementation (one to three times per week) appears to be as effective as

daily supplementation for preventing anemia at term and is better tolerated [2]. Gastrointestinal distress is common with 45 mg/day iron [3]. (See "Nutrition in pregnancy", section on 'Iron'.)

The multivitamin should also contain folic acid 0.4 to 0.8 mg to reduce the risk of open neural tube defects during the period of neural tube closure. Folic acid may have pregnancy benefits unrelated to prevention of neural tube defects, but available data are insufficient to support a clear benefit. (See "Folic acid supplementation in pregnancy".)

Diet — Nutrition, special diets, food safety, use of artificial sweeteners, as well as foods/supplements that should be consumed (eg, folic acid), limited (eg, caffeine), or avoided (eg, most herbal products, fish high in mercury (table 1)) are discussed in detail separately.

- (See "Nutrition in pregnancy".)
- (See "Fish consumption and docosahexaenoic acid (DHA) supplementation in pregnancy".)
- (See "Primary prevention of allergic disease: Maternal diet in pregnancy and lactation".)
- (See "The effects of caffeine on reproductive outcomes in women".)

Gestational weight gain — Recommendations for gestational weight gain are based on prepregnancy body mass index (table 2). Pregnancy is a risk factor for excessive weight gain, which increases future risks of cardiovascular disease and diabetes. Both excessive weight gain and obesity have been associated with an increased risk of cesarean delivery and macrosomia. Prenatal care is an important opportunity for discussing these risks and counseling about diet and exercise to achieve an appropriate weight gain. (See "Weight gain and loss in pregnancy" and "Obesity in pregnancy: Complications and maternal management".)

Healthy behaviors

Use of seat belts and air bags — Pregnant women should continue wearing three-point seat belts during pregnancy. The lap belt is placed across the hips and below the uterus; the shoulder belt goes between the breasts and lateral to the uterus. Although there are case reports of maternal and fetal injuries resulting from seat belt use, the overall effect is that seat belts provide significantly more benefit than risk to the mother and fetus in the event of collision [4,5].

There is less evidence regarding the effects of air bags. The largest study was a retrospective cohort study that assessed the effect of air-bag availability and air-bag deployment on the risk of adverse pregnancy outcome in over 3000 pregnant, front-seat occupants in motor vehicle crashes in Washington State [6]. Almost all of the women wore seat belts; two-thirds were in air bag equipped vehicles and one-third of the women were in vehicles without airbags. For the entire cohort, the authors did not find a statistically significant association between the presence of an air bag in the vehicle and risk of any adverse maternal or perinatal outcome in the event of a crash. When they compared only those crashes where an air bag deployed to those where it would have been likely to deploy if the vehicle was equipped with one, they found air bag deployment was associated with a trend toward increased preterm labor (relative risk [RR] 1.7, 95% CI 0.9-3.2), but not preterm birth (RR 0.8, 95% CI 0.3-1.9). The number of women with placental abruption or fetal death was too small to provide meaningful comparisons (abruption 4/198 with airbag deployed versus 10/622 without deployed air bag; fetal death 2/198 versus 2/622).

The American College of Obstetricians and Gynecologists (ACOG) recommends that pregnant occupants of motor vehicles wear lap and shoulder seatbelts and should not turn off air bags [7].

Oral health — Prevention, diagnosis, and treatment of oral conditions should not be deferred because of pregnancy. Dental radiographs (with shielding of the abdomen and thyroid) and procedures such as local anesthesia, dental extraction, root canal, restoration (amalgam or composite) of untreated caries, flossing, and scaling/planing of plaque/biofilm are not harmful to the fetus. As many dentists are reluctant to provide

care beyond routine cleaning in pregnancy, obstetricians should be willing to provide patients with letters or other references to support the provision of appropriate dental care.

Oral Health Care During Pregnancy: A National Consensus Statement is a helpful online resource that provides information by an expert workgroup convened by the Health Resources and Services Administration (HRSA) in collaboration with ACOG and the American Dental Association (ADA).

Avoidance of alcohol, cigarettes, and misuse of drugs — Maternal alcohol consumption, smoking, or misuse of drugs can be harmful to the fetus. Ideally, pregnant women will completely stop using these substances. Patients should be strongly advised of the risks of this behavior and referred to cessation or substitution programs in their area.

- (See "Alcohol intake and pregnancy".)
- (See "Cigarette and tobacco products in pregnancy: Impact on pregnancy and the neonate".)
- (See "Substance misuse in pregnant women".)
- (See "Methadone substitution therapy of opioid use disorder during pregnancy".)
- (See "Buprenorphine substitution therapy of opioid use disorder during pregnancy".)

Exercise and physical activity — For most pregnant women with uncomplicated pregnancies, the following exercise prescription is reasonable and part of a healthy lifestyle: moderate-intensity exercise (able to carry on a normal conversation during exercise) that includes aerobic exercise and strength training, performed for 30 minutes daily, five to seven days per week. Issues regarding type, frequency, and duration of exercise, as well as risks of and contraindications to exercise, are reviewed separately. (See "Exercise during pregnancy and the postpartum period".)

Although widely believed to improve some pregnancy outcomes, there is no high quality evidence that bed rest reduces the risk of miscarriage, preterm birth, or preeclampsia or improves pregnancy outcome in multiple gestation or impaired fetal growth [8-11]. Moreover, bed rest has known potential harms: It promotes loss of trabecular bone density, increases venous thromboembolism risk, produces musculoskeletal deconditioning, and places significant psychosocial strain on individuals and families [12-19].

Hot tubs, saunas, and pools — Hot tubs and saunas probably should be avoided during the first trimester because maternal heat exposure has been associated with an increased risk of neural tube defects. At a minimum, exposure should be short so that core temperature does not increase. (See "Open neural tube defects: Risk factors, prenatal screening and diagnosis, and pregnancy management", section on 'Fever/hyperthermia'.)

In a population-based study, swimming pool use did not appear to have any teratogenic effects despite exposure to water disinfection products and potential water-borne pathogens [20].

Precautions against infection — Some infections are potentially harmful in pregnancy and interventions should be taken to minimize the risk of these infections. In general, pregnant women should avoid contact with people with febrile illnesses that could be contagious and should practice good hygiene.

Immunization

- **Influenza** – Influenza vaccination is recommended for women who are or will be pregnant during the influenza season, regardless of stage of pregnancy. (See "Influenza and pregnancy", section on 'Vaccination'.)
- **Tetanus, diphtheria, pertussis** – Tetanus and diphtheria immunizations and boosters should be up-to-date. (See "Immunizations during pregnancy", section on 'Tetanus, diphtheria, and pertussis vaccination'.)

The tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine is administered in the third trimester of each pregnancy to protect the infant from pertussis, regardless of prior vaccination.

Preventive measures for other infections

- **Sexually transmitted infections** – Due to lack of need for contraception in pregnancy, many women do not consider use of condoms with sexual activity. For patients who may be at high risk of exposure (table 3) to sexually transmitted infections, clinicians should discuss condom use during pregnancy to reduce this risk.

- **Toxoplasmosis** – Prevention of primary infection is based upon avoidance of sources of infection, which include ingestion of contaminated undercooked or cured meat or meat products, soil-contaminated fruit or vegetables, or contaminated unfiltered water. (See "Toxoplasmosis and pregnancy", section on 'Prevention'.)

- **Cytomegalovirus** – Prevention of primary cytomegalovirus infections is based on good personal hygiene throughout pregnancy, especially hand washing with soap and water after contact with diapers or oral and nasal secretions (particularly with a child who is in daycare), not kissing children under age 6 on the mouth or cheek; not sharing food, drinks, or oral utensils with young children; and cleaning toys, countertops, and other surfaces that come into contact with children's urine or saliva. (See "Cytomegalovirus infection in pregnancy", section on 'Strategies for prevention of maternal and/or fetal infection'.)

- **Varicella** – Prevention is based on prepregnancy immunization and avoidance of significant exposure to varicella infection, which is highly contagious. The United States Advisory Committee on Immunization Practices recommends VariZIG, a varicella-zoster immune globulin preparation, in all nonimmune pregnant women who have been exposed to persons with varicella. (See "Varicella-zoster virus infection in pregnancy" and "Vaccination for the prevention of chickenpox (primary varicella infection)".)

- **Parvovirus** – Young children are the main source of respiratory-acquired parvovirus B19. The best measures to prevent maternal infection are good personal infection control practices, such as hand hygiene; not touching the eyes, mouth, or nose; avoiding close contact with sick individuals; and teaching children to cover the face with an elbow or tissue when sneezing or coughing. Many pregnant women have preexisting IgG to the virus, indicating immunity from a prior infection; those who are exposed to or have symptoms of parvovirus infection should have serologic testing for IgG and IgM antibodies and if acutely infected, they should be monitored for fetal effects. (See "Parvovirus B19 infection during pregnancy" and "Treatment and prevention of parvovirus B19 infection".)

- **Zika** – Given an association between Zika virus exposure during pregnancy and congenital microcephaly, pregnant women are advised to consider postponing travel to areas with ongoing mosquito transmission of Zika virus [21]. Women who must travel are advised to take precautions against mosquito bites including wearing long-sleeved shirts and pants, staying in places with air conditioning, sleeping under a mosquito net, and using approved insect repellant. In addition, pregnant women whose male partners have travelled to affected regions should abstain from sexual activity (vaginal, anal, and oral sex) or use condoms for the duration of the pregnancy. (See "Zika virus infection: Evaluation and management of pregnant women", section on 'Guidance for pregnant women'.)

- **Infections associated with pets** – Women who are pregnant or planning pregnancy should avoid contact with all rodents [22]. Precautions about handling pets and laboratory animals are discussed in topic reviews on each animal. Refer to topic reviews on zoonotic infection separately. (See "Zoonoses from cats" and "Zoonoses from dogs" and "Zoonoses from pets other than dogs and cats".)

- **Listeria and other foodborne infections** – To reduce the risk of foodborne illness, it is important that pregnant women: Practice good personal hygiene (frequent hand washing); consume only meats, fish, and poultry (including eggs) that are fully cooked; avoid unpasteurized dairy products and fruit/vegetable

juices; thoroughly rinse fresh fruits and vegetables under running water (about 30 seconds) before eating; avoid eating raw sprouts (including alfalfa, clover, radish, and mung bean); and wash hands, food preparation surfaces, cutting boards, dishes, and utensils that come in contact with raw meat, poultry, or fish with hot, soapy water. (See "Treatment, prognosis, and prevention of Listeria monocytogenes infection", section on 'Prevention of foodborne infection' and "Nutrition in pregnancy", section on 'Avoidance of foodborne infections'.)

Sleep position — The supine position in late pregnancy can decrease cardiac output and uterine perfusion due to aortocaval compression from the gravid uterus. The supine position during sleep in late pregnancy has been associated with an increased risk for stillbirth [23-26], but limitations of available studies include potential recall bias and confounding factors that may influence both sleep position, sleep pattern, and stillbirth. Pregnant women tend to avoid this position when awake because of associated symptoms (table 4), but it appears that many spend some time sleeping supine [27]. Further study is needed to determine if supine sleep truly plays a role in stillbirth, and whether education and intervention would be beneficial. (See "Maternal adaptations to pregnancy: Cardiovascular and hemodynamic changes", section on 'Postural hypotensive syndrome'.)

Common patient concerns

Risk of birth defects — The prevalence of birth defects of medical, surgical, or cosmetic significance is 2 to 4 percent among liveborn infants and does not vary among ethnic groups. Both genetic and environmental factors play a role in pathogenesis. (See "Birth defects: Causes".)

The clinician should discuss the causes of congenital anomalies with the patient, assess the specific risk for her child, review options for and limitations of prenatal diagnosis, and decide whether additional testing and referral to a geneticist would be useful.

Employment issues — A woman with an uncomplicated pregnancy who is employed where there are no greater potential hazards than those encountered in routine daily life may continue to work without interruption until the onset of labor. However, workplace safety and the physical demands of the woman's job should be considered, especially in women at higher risk of preterm delivery. (See "Working during pregnancy".)

Sexual activity — Theoretically, sexual intercourse may stimulate labor due to physical stimulation of the lower uterine segment, endogenous release of oxytocin as a result of orgasm, direct action of prostaglandins in semen, or increased exposure to infectious agents. However, in the absence of pregnancy complications (eg, vaginal bleeding, ruptured membranes), there is insufficient evidence to recommend against sexual intercourse during pregnancy. Most studies have not shown an increased risk of preterm labor/delivery or infectious complications, unless a sexually transmitted disease is acquired [28,29].

Travel — Pregnant women who travel need to consider several issues, including:

- Their risk of pregnancy complications away from their usual source of medical care, as well as the availability of medical resources and their medical insurance coverage at their destination.
- The increased risk of venous thromboembolism during pregnancy and with prolonged immobility during the trip.
- Issues related to air travel (eg, access to medical providers, lower oxygen environment, restricted movement). (See 'Airline travel' below.)
- The potentially increased risk of exposure to infectious diseases (eg, travelers' diarrhea, malaria, Zika virus), as well as prophylaxis, prevention and treatment of these diseases. Given the association between Zika virus during pregnancy and congenital microcephaly, pregnant women should consider postponing travel to areas with mosquito-borne Zika virus transmission. (See "Zika virus infection:

Evaluation and management of pregnant women" and "Prevention and treatment of malaria in pregnant women".)

Airline travel — Most airlines allow women to fly up to 37 weeks of gestation, although individual policies may vary. Commercial airline travel is generally safe for women with uncomplicated pregnancies [30-33]. Fetal heart rate is not affected during flight if the mother and fetus are healthy [31]. Observational studies have reported an increased risk of miscarriage in flight attendants (odds ratio [OR] 1.62, 95% CI 1.29-2.04) and an increased risk of preterm birth among passengers (OR 1.44, 95% CI 1.07-1.93) [34], particularly women who fly for long durations and frequently [35]. In contrast to passengers, flight attendants do not appear to have an increased risk of preterm birth [34]. These findings could be due to failure to account for relevant differences between study subjects and controls.

Maternal physiologic adaptations to high altitude include hemoconcentration, increased heart rate and blood pressure, and decreased aerobic capacity with reduction of partial oxygen pressure [31,36]. For these reasons and the lack of availability of emergency care, certain precautions should be taken during air travel [32]:

- Women with complicated pregnancies that may be exacerbated by flight conditions or require emergency care should avoid air travel.
- All airline travelers should maintain hydration and periodically move their lower extremities to minimize stasis and reduce the risk of venous thrombosis; use of compression stockings and avoidance of restrictive clothing may also be helpful. Seat belts should be worn continuously to protect against injury from unexpected turbulence.
- Supplemental oxygen should be administered to pregnant women (eg, women with sickle cell disease, severe anemia [hemoglobin <8 g/dL], or cyanotic heart disease) who must travel and may not tolerate the relatively hypoxic environment of high altitude flying, even in pressurized aircraft. (See "Traveling with oxygen aboard commercial air carriers".)

The amount of cosmic radiation received during airline travel is below the level at which there begins to be concern about possible harmful fetal effects (20 millisievert or 2 rem) [37]. As an example, a woman on a round trip transpolar flight from New York to Tokyo would be exposed to approximately 15 mrem cosmic radiation; for a round trip transcontinental flight across the United States, the exposure would be 6 mrem. By comparison, the International Commission on Radiological Protection (ICRP) and the National Council on Radiation Protection (NCRP) recommended limit for maximum cumulative radiation exposure for a member of the general public over one year is 100 mrem [38,39]. Pilots, flight attendants, and frequent fliers might exceed this level, particularly if they fly during solar particle events, when radiation levels can increase significantly. They should be aware of their personal radiation exposure, which can be calculated using the Federal Aviation Administration Radiobiological Team web site. A detailed discussion of radiation risks in pregnancy can be found separately. (See "Diagnostic imaging procedures during pregnancy".)

Long-distance airline travel also disrupts circadian rhythms; the effects of this on pregnancy are unknown.

Travel to moderate and high altitudes — Airplane passenger cabins are usually pressurized to an altitude of 5000 to 8000 ft (1524 to 2438 m). The PO_2 values at these altitudes are 132 and 118 mmHg, respectively (table 5) [36]. Pregnant women may be exposed to altitudes in this range from other sources, such as visiting a mountain resort or traveling in a hot air balloon or noncommercial aircraft. There is scant literature about acute, short-term exposure of pregnant women to these moderate altitudes. One study evaluated seven women in the third trimester at sea level (180 ft) and then within two to four days of visiting a facility at 6000 ft (1829 m) [36]. Plasma glucose rose from 4.53 to 5.51 mmol/L (81.6 to 99.2 mg/dL); maternal heart rate, oxygen consumption, ventilation, tidal volume, and plasma catecholamine and lactate levels did not change significantly, nor was there a change in fetal heart rate.

These data and other reports [40,41], although limited, are reassuring that women with uncomplicated pregnancies can tolerate acute exposure to moderate altitudes. Since an individual's altitude tolerance cannot be reliably determined at sea level, advice on travel to intermediate altitudes should err on the side of caution [40,41].

High altitudes (over 8000 ft [2438 m]) are more likely to cause problems. In general, exposure of a pregnant woman to the hypoxia of high altitude results in acclimatization responses, which preserve the fetal oxygen supply. The fetus also can utilize some compensatory mechanisms during brief periods of hypoxia. However, these adaptive mechanisms may not be fully compensatory in complicated pregnancies, such as those with uteroplacental insufficiency, or at very high altitudes [42]. As an example, pregnancy in inhabitants of Cerro de Pasco, Peru (altitude 14,337 ft [4370 m]) is associated with 31 percent lower maternal cardiac output and 11 percent lower birthweight than observed in pregnant women residing at sea level (mean birth weight 2935 and 3290 g, respectively) [43].

A survey of obstetrical care providers in Colorado reported that preterm labor and bleeding complications of pregnancy were the most commonly encountered pregnancy complications among pregnant visitors to high altitudes [44]. Dehydration, engaging in strenuous exercise before acclimatization, and participation in activities with high risk of trauma were behaviors that could increase the risk of pregnancy complications. Some experts suggest that an altitude of 8000 ft should not be exceeded in the first few days of short-term exposure to high altitude [40]. (See "High altitude illness: Physiology, risk factors, and general prevention".)

Hair dyes and other cosmetic products — Exposure to hair dyes or hair grooming/styling products results in very limited systemic absorption, unless the integrity of scalp skin is compromised by disease. Therefore, these chemicals are unlikely to cause adverse fetal effects in women with a normal scalp [45,46]. Although adverse effects have been reported, data on safety are limited, inconsistent, and based on maternal self-report [47-49]. We tell patients that plant-based hair dyes are probably safe and there is no information on whether non-ammonia versus ammonia-based products are safer. A prudent approach is to avoid ammonia- and peroxide-based products, given the wide availability of non-ammonia-based products. We also tell patients to use these products in a well-ventilated area since women with asthma/allergies may be more sensitive to the scents during pregnancy. Lastly, it is prudent to avoid new products since skin sensitivity is more common in pregnancy.

There are also only limited data on the safety of cosmetics. As above, skin may be more sensitive in pregnancy. Some nail polishes have toluene, formaldehyde, and dibutyl phthalate. Theoretically, these toxins may be inhaled when applied or absorbed from the nail bed, so it is prudent to apply nail polish in a well ventilated place.

Shortness of breath — Pregnancy is a state of relative hyperventilation, which may be centrally mediated through progesterone. The respiratory rate does not change while tidal volume increases, resulting in an approximately 50 percent increase in minute ventilation, which accounts for the feeling of shortness of breath. Physiologic dyspnea of pregnancy is of gradual onset: Sudden onset or presence of cough, wheezing, rales, chest pain, fever, or hemoptysis suggests a pathologic process that requires further evaluation. (See "Maternal adaptations to pregnancy: Physiologic respiratory changes and dyspnea", section on 'Evaluation of pregnant women with dyspnea'.)

Airborne pollutants — Numerous studies have examined potential associations between various airborne pollutants and adverse outcomes, such as low birth weight, preterm birth, and small for gestational age birth and have come to different conclusions because of difficulties in measuring exposures, timing of measurements, and degree of adjustment for confounding. (See "Overview of occupational and environmental risks to reproduction in females", section on 'Airborne pollutants'.)

Use of insect repellants — The CDC has advised pregnant women to take precautions to reduce their risk of acquiring arboviral infections (eg, Zika virus, West Nile virus) by avoiding mosquito bites through use of protective clothing (including permethrin-treated) and DEET (N,N-diethyl-3-methylbenzamide)-based

repellents [50]. Topically-applied DEET does not pose hazards to the developing fetus, regardless of gestational age. (See "Prevention of arthropod and insect bites: Repellents and other measures", section on 'Pregnant women' and "Prevention of arthropod and insect bites: Repellents and other measures", section on 'Permethrin-treated clothing'.)

Stretch marks and other normal changes of skin, nails, and hair — (See "Maternal adaptations to pregnancy: Skin, hair, nails, and mucous membranes".)

Tattoos and body piercing — (See "Maternal adaptations to pregnancy: Skin, hair, nails, and mucous membranes", section on 'Tattoos and piercing'.)

Management of common discomforts

Nausea and vomiting — (See "Clinical features and evaluation of nausea and vomiting of pregnancy" and "Treatment and outcome of nausea and vomiting of pregnancy".)

Gastroesophageal reflux disease — (See "Medical management of gastroesophageal reflux disease in adults", section on 'Pregnancy and lactation'.)

Constipation — Increasing dietary fiber and fluids or using bulk-forming laxatives is the preferred treatment of constipation during pregnancy since these agents are not absorbed. For refractory cases, occasional use of magnesium hydroxide, lactulose, or bisacodyl is probably not harmful as magnesium salts have been widely used in pregnancy with a good safety profile and lactulose and bisacodyl, although not studied in human pregnancy, are minimally absorbed. Castor oil can stimulate uterine contractions and excessive use of mineral oil can interfere with absorption of fat soluble vitamins, so these agents are generally avoided. (See "Management of chronic constipation in adults".)

Hemorrhoids — (See "Maternal adaptations to pregnancy: Gastrointestinal tract", section on 'Hemorrhoids' and "Home and office treatment of symptomatic hemorrhoids".)

Rhinitis and epistaxis — (See "An overview of rhinitis", section on 'Rhinitis of pregnancy' and "Approach to the adult with epistaxis".)

Gingivitis — Most pregnant women also note gingival changes and/or gingivitis (picture 1). These changes consist of enlargement and blunting of the interdigital papillae, which may result in gingival bleeding, ulceration, and pain. In addition to good oral hygiene, therapy for pregnancy gingivitis involves debridement and possibly adjunctive antibiotics. (See "Gingivitis and periodontitis in adults: Classification and dental treatment", section on 'Pregnancy gingivitis'.)

Difficulty sleeping — Sleep during pregnancy, especially late pregnancy, is fragmented and characterized by increased waking after sleep onset, greater amounts of light sleep, and less deep sleep [51-53]. Some reasons for this include nocturia, nocturnal gastroesophageal reflux, anxiety, restless legs or leg cramps, low back pain, physical limitations in achieving a comfortable position, and, primarily in obese women, obstructive sleep apnea. (See "Obstructive sleep apnea in pregnancy".)

In the absence of treatment for a specific medical condition, such as gastroesophageal reflux disease, suggestions for better sleep include maintaining a regular sleep schedule in a low stimuli environment; cutting down on the amount of liquids in the hours before bedtime; avoiding caffeine after noon; exercising regularly for at least 20 minutes at least a few hours before bedtime; placing pillows between the knees, under the abdomen, and behind the back to take pressure off the lower back; putting a night light in the bathroom to avoid turning on a bright light, which tends to increase wakefulness; using relaxation techniques; and avoiding naps late in the day [54].

We do not prescribe sleep medication for pregnant women. Sedating antihistamines (eg, doxylamine, diphenhydramine) or zolpidem have been used for short-term treatment of sleeplessness in pregnancy. A 2015 systematic review and meta-analysis of 16 studies evaluated the use of benzodiazepines, hypnotic

benzodiazepine receptor agonists, antidepressants, and antihistamines in pregnant women with sleep disturbances [55]. Overall, the studies reported no correlation between use of these medications and risk of congenital anomalies. Benzodiazepines and hypnotic benzodiazepine receptor agonist use may increase the rates of preterm birth, low birth weight, and small for gestational age infants, but available studies were prone to bias. There is also concern that transplacental passage of these medications may cause neonatal respiratory depression. Although the meta-analysis was limited by the small number of studies, study design (most were cohort studies), and small numbers of included subjects, it generally supports avoiding such medications in pregnancy.

Headache — (See "Headache in pregnant and postpartum women".)

Back pain and sciatica — (See "Maternal adaptations to pregnancy: Musculoskeletal changes and pain", section on 'Low back pain and disc disease'.)

Leg cramps — (See "Maternal adaptations to pregnancy: Musculoskeletal changes and pain", section on 'Leg and foot pain'.)

Peripheral edema — Water retention is a physiological phenomenon in pregnancy, with an average increase at term of 3 L. Water retention is clinically evident as edema of the ankles and legs, a normal finding in a large proportion of pregnant women near term. A fall in plasma osmolality of 10 mosmol/kg is one of the main reasons for water retention. Antidiuretic hormone release and the osmotic threshold for thirst decrease in parallel resulting in water retention [56].

Interventions that may prevent or reduce edema include not standing for long periods of time, resting/sleeping on the left side, wearing support hose or compression stockings, and water immersion.

Varicose veins — Pregnancy is a risk factor for development of varicose veins, which may become symptomatic anytime during the antepartum or postpartum period. Compression stockings do not prevent varicose veins, but may relieve symptoms [57]. (See "Overview and management of lower extremity chronic venous disease" and "Vulvovaginal varicosities and pelvic congestion syndrome".)

Diarrhea — The management of patients with acute diarrhea initially involves general supportive measures such as hydration and alteration of diet. Loperamide was not teratogenic in animal studies, but human data are conflicting [58]. Antibiotic therapy is rarely needed since the illness is usually self-limited and most often viral in etiology. (See "Approach to the adult with acute diarrhea in resource-rich settings".)

Urinary frequency and nocturia — Urinary frequency (voiding >7 times per day) and nocturia (voiding ≥2 times at night) are among the most common pregnancy-related complaints, affecting 80 to 95 percent of women at some point during gestation [59-61]. Frequency appears to be due in part to changes in bladder function and in part to a small increase in urine output. Urinary frequency typically begins in the first trimester; thus, mechanical compression of the bladder by the enlarged uterus is not likely to be the primary cause. Nocturia is common and increases with advancing gestation, which may be partially attributable to nocturnal mobilization of dependent edema. Supportive care includes avoiding caffeine and avoiding consumption of fluids two to three hours before bedtime. (See "Maternal adaptations to pregnancy: Renal and urinary tract physiology", section on 'Symptoms'.)

True polyuria, defined as urine output exceeding 3 L/day, is not physiologic and may be due to transient diabetes insipidus of pregnancy, which is a rare, but important cause of pathologic polyuria. (See "Polyuria and diabetes insipidus of pregnancy".)

SAFETY OF SELECTED COMMON MEDICATIONS USED TRANSIENTLY IN PREGNANCY

Overview — Medication use is common in pregnancy [62-67]. However, information about known or potential maternal or fetal adverse reactions and dose adjustments needed during pregnancy and the postpartum period is very limited because pregnant women are generally not included in studies to determine safety and efficacy of new medications. It has been estimated that sufficient information to determine risk for birth

defects is available for <10 percent of medications approved by the US Food and Drug Administration (FDA) since 1980 [68].

The following general principles apply to use of medication during pregnancy:

- Avoid fetal drug exposure, when possible. The first trimester especially since it is the major period of organogenesis, but fetal exposure to drugs later in gestation can also result in subtle morphologic abnormalities, functional abnormalities, and impairment in growth.
- When a medication needs is to be taken, discuss with patients the risks and benefits of taking versus not taking the drug, citing the best available evidence. Information on the use of specific drugs in pregnancy is available in the UpToDate drug database, as well as in topics that review treatment of medical conditions in pregnant women. Other resources include:
  - Reproductive Toxicology Center

    REPROTOX

    Columbia Hospital for Women Medical Center

    Washington, DC

    202-293-5137
  - Teratogen Information System

    TERIS and Shepard's Catalog of Teratogenic Agents

    Seattle, WA

    206-543-2465
  - Pregnancy Exposure Registries
  - Organization of Teratology Information Specialists (OTIS)

    877-311-8972
  - Motherisk

    The Hospital for Sick Children

    Toronto, Canada

    877-439-2744
  - The Teratology Society

    The Teratology Society publishes a free teratology primer
- When prescribing drugs, minimize the number of medications taken, limit use of medication to situations where the benefit clearly outweighs the risk, choose medications with the best safety profile, and use them at the lowest dose and for the shortest duration that is effective. Older medications with good safety records are generally preferable to newer medications since pregnancy data on newer drugs is usually very limited or nonexistent.
- Inform patients to contact their provider with any medication concerns and before stopping a drug or starting a new drug (prescription, over-the-counter, or herbal [alternative] remedies).

Women exposed to drugs of uncertain safety in the first trimester can be offered ultrasound examination at 18 to 20 weeks of gestation to screen for fetal anatomic abnormalities, with fetal echocardiography if congenital heart disease is suspected. (See "Routine prenatal ultrasonography as a screening tool" and "Fetal cardiac abnormalities: Screening, evaluation, and pregnancy management".)

Pain and fever medications

Acetaminophen — Acetaminophen is a widely used for treatment of pain and fever, with no high-quality evidence in humans of increased risk of pregnancy loss, congenital anomalies, or neurodevelopmental delay [69,70]. Epidemiologic studies have reported an association between in utero acetaminophen exposure and risk of attention-deficit/hyperactivity disorder (ADHD)-like behaviors at ages 7 and 11 years [71-73]. However, the absolute risk was small and these studies have several methodologic limitations including a lack of assessment of overall health for the index pregnancy, lack of information on acetaminophen strength and dosage units taken, and lack of formal assessment of attention deficit hyperactivity disorder.

A 2015 US Food and Drug Administration Drug Safety Communication assessed the available evidence to be inconclusive regarding a possible connection between acetaminophen use in pregnancy and ADHD in children [74]. Similarly, a 2017 review by the Society for Maternal-Fetal Medicine reported that no conclusion could be made regarding a possible causal association between maternal acetaminophen use and neurobehavioral issues because of aforementioned study limitations [75]. Subsequent to these communications, a study from Norway that adjusted for maternal use of acetaminophen before pregnancy, familial risk for ADHD, and indications of acetaminophen use reported an increased risk of ADHD with acetaminophen use >29 days: HR 2.20 (95% CI 1.50-3.24), while use for <8 days was negatively associated with ADHD: HR 0.90 (95% CI 0.81-1.00) [76]. Moreover, paternal and maternal use of acetaminophen were similarly associated with ADHD. These data may reassure women who require only a few doses of acetaminophen for treatment of fever or pain during pregnancy.

Epidemiologic studies have also suggested a small, but statistically significant, association between maternal use of mild analgesics and cryptorchidism in offspring, particularly second trimester or prolonged exposure [77-79]. Acetaminophen may also reduce fetal testosterone production. These findings are subject to the many limitations of observational studies and should not change practice, but they provide impetus for further research [74,80]. As with most other drugs, it is reasonable to avoid prolonged use of acetaminophen in pregnancy, if possible, until more data are available. Since descent of the testes occurs in late gestation, first trimester avoidance of acetaminophen will not address this potential problem.

It is possible that reduction of fever with acetaminophen reduces the risk of some birth defects, but further study is needed [70]. The extensive use of acetaminophen by pregnant women combined with the paucity of documented adverse effects has served to make this medication the pain reliever and antipyretic of choice during pregnancy when short-term drug therapy is indicated [81].

However, it is important to caution patients against excessive use of acetaminophen. The therapeutic dose is 325 to 1000 mg per dose in adults, with a usual maximum recommended daily dose of about 3 g for oral immediate release preparations. Accidental overuse may be more likely in pregnancy due to limitations on use of other medications and perceptions of its safety. Limited data suggest good fetal outcomes in cases of maternal overdose/overuse, but potential for maternal morbidity is high. (See "Acetaminophen (paracetamol) poisoning in adults: Pathophysiology, presentation, and diagnosis" and "Acetaminophen (paracetamol) poisoning in adults: Treatment", section on 'Treatment in pregnancy'.)

NSAIDs — The risks and benefits of using nonsteroidal antiinflammatory drugs (NSAIDs) for treatment of pain or fever depend on the dose, gestational age, and duration of therapy. These risks are discussed in detail separately. Importantly, use of NSAIDs other than low dose aspirin for more than 48 hours can cause in utero constriction of the ductus arteriosus as early as 24 weeks of gestation, but is most common after 31 to 32 weeks. (See "Safety of antiinflammatory and immunosuppressive drugs in rheumatic diseases during pregnancy and lactation" and "Inhibition of acute preterm labor", section on 'Cyclooxygenase inhibitors'.)

Opioids — There is limited information on the effects of long-term (≥1 month) prescription opioid use during pregnancy. Neonatal withdrawal syndrome is a major concern when the mother has used opioids long-term and in the week prior to delivery. (See "Neonatal abstinence syndrome".)

The safety of short-term opioid use is also unclear. Data from an animal study support an association between maternal opioid use and central nervous system defects in offspring [82]. Three epidemiologic studies in humans have also reported an association with neural tube defects, with odds ratios of 1.7 to 2.9 [83-85]. An association has also been reported between opioid use in pregnancy and congenital heart defects, and gastroschisis; preterm delivery, poor fetal growth, and stillbirth [83,86]. In most cases, opioids were used for short-term analgesia. Limitations of these studies include that exposure information was based on maternal recall up to one year after delivery, information on drug dose and duration was not obtained, the drugs were used to treat pain from a wide variety of disorders, many of the narcotics were part of a multi-component drug regimen, congenital abnormalities in pregnancy losses were not ascertained, and the possibility of chance associations is increased when multiple comparisons are made. Even in the large studies, the number of cases was small and subject to selection bias. A 2015 US FDA Safety Announcement stated further investigation of this issue is needed before we can determine whether the weight of evidence supports the presence of an increased risk of neural tube defects related to opioid exposure in early pregnancy [74]. The absolute risk of open neural tube defects is low in the United States, about three per 10,000 live births. Therefore, if a true causal relationship exists, a twofold increase in risk would represent a small increase in the absolute risk of open neural tube defects.

Until better data are available, during the first month of embryonic development when neural tube development occurs, shared decision-making involves balancing the small potential increase in incidence of neural tube defects with the need for relief of moderate to severe pain, given the frequent lack of effective alternative analgesics.

Issues related to methadone and nonprescription opioids are reviewed separately. (See "Substance misuse in pregnant women" and "Methadone substitution therapy of opioid use disorder during pregnancy" and "Buprenorphine substitution therapy of opioid use disorder during pregnancy".)

Antibiotics — Antibiotics without known teratogenic effects include: the cephalosporins, penicillins, erythromycin (except the estolate), azithromycin, clindamycin, augmentin, and metronidazole.

An association between spontaneous abortion and first trimester use of macrolides (excluding erythromycin), quinolones, tetracyclines, sulfonamides, and metronidazole was observed in a nested case control study including over 95,000 pregnant women [87]. Confounding by indication and unmeasured confounders could account for these results.

The following antibiotics have been associated with known or potential teratogenic effects:

- **Aminoglycosides** carry a risk of fetal (and maternal) ototoxicity and nephrotoxicity, but not with structural birth defects.
- Doxycycline – Tetracyclines are generally contraindicated in pregnancy because of the risk of hepatotoxicity in the mother [88] and adverse effects on fetal bone and teeth (eg, permanent discoloration of deciduous teeth from in utero exposure in the second and third trimesters [89], incorporation into fetal long tubular bones with transient inhibition of growth [90]). However, these events are extremely rare with doxycycline, and subsequent evidence in both pregnancy and in children has supported the relative safety of doxycycline compared with older tetracyclines [91,92]. As an example, in a systematic review, there was no correlation between the use of doxycycline and teratogenic effects during pregnancy or dental staining in children [91].
- **Fluoroquinolones** – Fluoroquinolones are generally avoided during pregnancy and lactation because they are toxic to developing cartilage in experimental animal studies. However, neither adverse effects

on cartilage nor an increase in congenital malformations from use during human pregnancy has been documented [93].

- Trimethoprim – Trimethoprim is generally avoided in the first trimester because it is a folic acid antagonist [94-96], has caused abnormal embryo development in experimental animals, and some case control studies have reported a possible association with a variety of birth defects [69]. However, it is not a proven teratogen in humans. Additional evaluation of the safety of trimethoprim in human pregnancy is needed. The safest course is to avoid using trimethoprim in the first trimester if another antibiotic that is safe and effective is available. If exposure does occur, we advise patients of the baseline risk of birth defects in the population and the possibility of a low, but unproven increase in risk of birth defects after exposure to trimethoprim.

- **Sulfonamides,** nitrofurantoin – The safest course is to avoid using nitrofurantoin or sulfonamides in the first trimester if another antibiotic that is safe and effective is available, but use of these drugs is appropriate when good alternatives are not available, based on the data discussed below [97]. Both drugs have been implicated to cause hemolysis in women with glucose-6-phosphate dehydrogenase deficiency and those at risk for this condition (table 6), although the literature contains conflicting information. (See "Diagnosis and management of glucose-6-phosphate dehydrogenase (G6PD) deficiency", section on 'Inciting drugs, foods, illnesses'.)

  A National Birth Defects Prevention (NBDP) Study reported statistically significant associations between a variety of birth defects and use of sulfonamides or nitrofurantoin [98]. In addition, a previous small case-control study reported a statistically significant association between nitrofurantoin use and cardiac defects (odds ratio 1.7) [99]. These findings should be interpreted with caution because both studies were retrospective. In the NBDP study, multiple comparisons involving small numbers of affected exposed infants may have led by chance to the observed small increase in odds ratios. For each birth defect, only between 4 and 21 infants were exposed to one of the antibiotics and some patients in the study were exposed to more than one potential teratogen. For both studies, long periods between the exposure and patient interviews (six weeks to two years), recall bias, and inability to determine if the birth defects were related to the infection rather than the treatment further limit these findings. In contrast, a population-based cohort study from Norway found no significant association between filling a nitrofurantoin prescription in the first trimester and risk of congenital malformations (all, major, or cardiovascular) [100].

  Sulfonamides compete with bilirubin for albumin binding sites and theoretically may increase the risk of kernicterus at low bilirubin levels. For this reason, these drugs have been avoided near delivery if another antibiotic is available. However, a systematic review found no cases of kernicterus associated with maternal use of sulfonamides during pregnancy or lactation [101]. A subsequent study reported the presumed association between maternal use of sulfamethizole and neonatal jaundice was the result of preterm birth; the association became insignificant when data were adjusted for gestational age [102]. Another study described an increased risk of kernicterus in preterm infants administered sulfisoxazole for antibiotic prophylaxis [103].

Cold and allergy medications — Use of over-the-counter and prescription drugs for treatment of respiratory infections and allergies in pregnancy is discussed in detail elsewhere. (See "Treatment of respiratory infections in pregnant women" and "Recognition and management of allergic disease during pregnancy".)

PREPARATION FOR LABOR, DELIVERY, AND THE PUERPERIUM

- (See "Preparation for labor and childbirth".)
- (See "Breastfeeding: Parental education and support".)
- (See "Postpartum contraception: Initiation and methods".)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Prenatal care (The Basics)" and "Patient education: Activity during pregnancy (The Basics)")
- Beyond the Basics topics (see "Patient education: Avoiding infections in pregnancy (Beyond the Basics)" and "Patient education: Should I have a screening test for Down syndrome during pregnancy? (Beyond the Basics)" and "Patient education: Group B streptococcus and pregnancy (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Patient education and health promotion are important components of prenatal care and involve discussion of a number of subjects. (See 'Patient education and health promotion' above.)
- The following general principles apply to use of medication during pregnancy (see 'Safety of selected common medications used transiently in pregnancy' above):
  - Avoid fetal drug exposure, when possible – the first trimester especially since it is the major period of organogenesis, but fetal exposure to drugs later in gestation can also result in subtle morphologic abnormalities, functional abnormalities, and impairment in growth.
  - When a medication needs is to be taken, discuss with patients the risks and benefits of taking versus not taking the drug, citing the best available evidence. Information is available from several resources.

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Topic 112420 Version 19.0

GRAPHICS

FDA advice on fish consumption in women who are pregnant, might become pregnant, or are nursing

Best choices (eat two to three servings a week)		
▪ Anchovy ▪ Atlantic croaker ▪ Atlantic mackerel ▪ Black sea bass ▪ Butterfish ▪ Catfish ▪ Clam ▪ Cod ▪ Crab ▪ Crawfish ▪ Flounder ▪ Haddock	▪ Hake ▪ Herring ▪ Lobster, American and spiny ▪ Mullet ▪ Oyster ▪ Pacific chub mackerel ▪ Perch (freshwater and ocean) ▪ Pickerel ▪ Plaice ▪ Pollock ▪ Salmon ▪ Sardine	▪ Scallop ▪ Shad ▪ Shrimp ▪ Skate ▪ Smelt ▪ Sole ▪ Squid ▪ Tilapia ▪ Trout (freshwater) ▪ Tuna, canned light (includes skipjack) ▪ Whitefish ▪ Whiting
Good choices (eat one serving a week)		
▪ Bluefish ▪ Buffalofish ▪ Carp ▪ Chilean sea bass/Patagonian toothfish ▪ Grouper ▪ Halibut ▪ Mahi mahi/dolphinfish	▪ Monkfish ▪ Rockfish ▪ Sablefish ▪ Sheepshead ▪ Snapper ▪ Spanish mackerel ▪ Striped bass (ocean)	▪ Tilefish (Atlantic Ocean) ▪ Tuna, albacore/white tuna, canned and fresh/frozen ▪ Tuna, yellowfin ▪ Weakfish/sea trout ▪ White croaker/Pacific croaker
Choices to avoid (highest mercury levels)		
▪ King mackerel ▪ Marlin ▪ Orange roughy ▪ Shark	▪ Swordfish ▪ Tilefish (Gulf of Mexico) ▪ Tuna, bigeye	

Note: On average, farm-raised fish tend to be lower in mercury compared with wild-caught fish.[1]

Reference:

1. *Karimi R, Fitzgerald TP, Fisher NS. A quantitative synthesis of mercury in commercial seafood and implications for exposure in the United States. Environ Health Perspect 2012; 120:1512.*

Reproduced from: U.S. Food and Drug Administration. Food: Eating Fish: What Pregnant Women and Parents Should Know. Available at: http://www.fda.gov/Food/FoodborneIllnessContaminants/Metals/ucm393070.htm (Accessed January 26, 2017).

Graphic 111607 Version 3.0

Recommendations for total and rate of weight gain during pregnancy by prepregnancy BMI

	Total weight gain		Rates of weight gain* second and third trimester	
Prepregnancy BMI	**Range in kg**	**Range in lb**	**Mean (range) in kg/week**	**Mean (range) in lb/week**
Underweight (<18.5 kg/m^2)	12.5 to 18	28 to 40	0.51 (0.44 to 0.58)	1 (1 to 1.3)
Normal weight (18.5 to 24.9 kg/m^2)	11.5 to 16	25 to 35	0.42 (0.35 to 0.50)	1 (0.8 to 1)
Overweight (25.0 to 29.9 kg/m^2)	7 to 11.5	15 to 25	0.28 (0.23 to 0.33)	0.6 (0.5 to 0.7)
Obese (≥30.0 kg/m^2)	5 to 9	11 to 20	0.22 (0.17 to 0.27)	0.5 (0.4 to 0.6)

BMI: body mass index.

* Calculations assume a 0.5 to 2 kg (1.1 to 4.4 lb) weight gain in the first trimester.

Weight Gain During Pregnancy: Reexamining the Guidelines. Institute of Medicine (US) and National Research Council (US) Committee to Reexamine IOM Pregnancy Weight Guidelines, Rasmussen KM, Yaktine AL (Eds), National Academies Press (US), The National Academies Collection: Reports funded by National Institutes of Health, Washington (DC) 2009. Reprinted with permission from the National Academies Press, Copyright © 2009 National Academy of Sciences.

Graphic 75820 Version 17.0

Women at increased risk of having a sexually transmitted infection

- Personal history of a prior sexually transmitted infection
- Age <25 years
- New sex partner in past 60 days
- More than one sex partner or sex partner with multiple concurrent sex partners
- Sex partner diagnosed with a sexually transmitted infection
- No or inconsistent condom use outside a mutually monogamous sexual partnership
- Trading sex for money or drugs
- Sexual contact with sex workers
- Meeting anonymous partners on the internet
- Unmarried status
- Lower socioeconomic status or high school education or less
- Admission to correctional facility or juvenile detention center
- Use of illicit drugs
- Living in a community with a high prevalence of sexually transmitted infections

Graphic 112388 Version 1.0

Signs and symptoms attributed to supine hypotensive syndrome in pregnancy

Faintness
Dyspnea
Dizziness
Restlessness
Nausea
Vomiting
Chest pain
Abdominal pain
Visual disturbances
Numbness
Paresthesias
Headache
Cold, clammy skin
Pallor
Cyanosis
Hypotension

Graphic 80135 Version 1.0

Physical effects of change in altitude

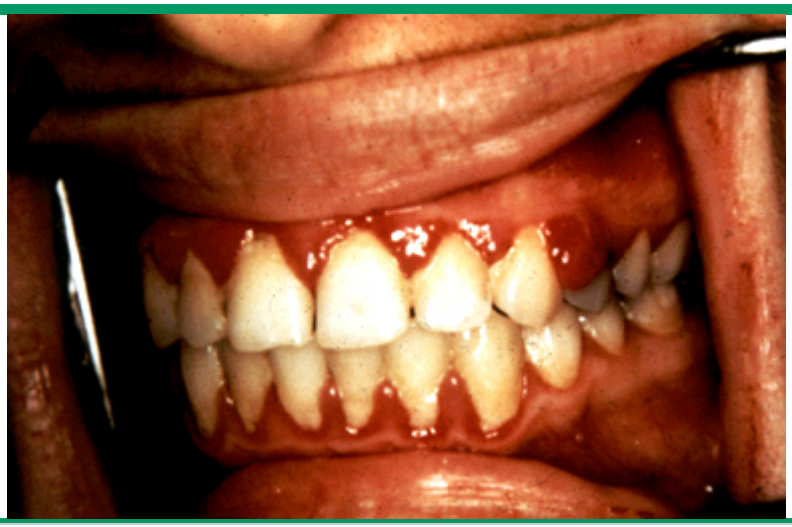
Altitude, feet	Barometric pressure, mmHG	Atmospheric P02, mmHG	PI02, mmHG	PA02, mmHG	Pa02, mmHG
0	760	159	149	103	98
2000	707	148	138	94	90
4000	656	137	128	85	80
5000	632	132	122	81	66
6000	609	127	117	77	64
8000	564	118	108	69	60
10000	523	109	100	61	53

PI02: partial pressure of inspired oxygen; PA02: partial pressure of alveolar oxygen; Pa02: partial pressure of oxygen in arterial blood 8000 feet represents the maximum allowable altitude in commercial aircraft.

Adapted from Gong, H. Exposure to moderate altitude and cardiorespiratory diseases. Cardiologica 1995; 40:477.

Graphic 63773 Version 2.0

Gingivitis during pregnancy



Hormonal changes that occur with pregnancy significantly influence the bacterial flora, causing significant gingival inflammation and hypertrophy.

Courtesy of Mark S Obernesser, DDS, MMSc.

Graphic 82278 Version 1.0

Partial list of medicines and other substances thought to be unsafe or safe in individuals with G6PD deficiency

Medicines and other substances likely to be UNSAFE in moderate to severe G6PD deficiency (WHO classes I, II, and III*)[1-3]
Anti-infectives
Dapsone
Nitrofurantoin and related, including nifuratel[¶] and nitrofurazone (nitrofural)[¶]
Primaquine
Miscellaneous
Dimercaprol[Δ]
Methylene blue (methylthioninium chloride) (antidote, also contained in some urinary tract combination products)
Phenazopyridine (pyridium)
Toluidine blue (tolonium chloride) (diagnostic agent)
Uricase (rasburicase, pegloticase)
Chemical exposures and foods likely to be UNSAFE in moderate to severe G6PD deficiency (WHO classes I, II, and III)
Aniline dyes
Naphthalene (mothballs, lavatory deodorant)
Henna compounds (black and red Egyptian) and related dyes used for hair and tattoos
Fava beans
Some prefer to avoid red wine, legumes, blueberries, soya, and tonic water[4]
Medicines previously considered unsafe, but PROBABLY SAFE given in usual therapeutic doses in G6PD deficiency (WHO classes II and III); NOTE: safety in WHO Class I G6PD deficiency is generally not known[2]
Analgesics
Acetaminophen (paracetamol)
Antipyrine (phenazone)
Aspirin (acetylsalicylic acid)
Aminophenazone[¶] and related NSAIDs (dipyrone[¶], metamizole[¶])
Anti-infectives
Antimalarials: chloroquine, mepacrine, quinine
Fluoroquinolones[Δ]: ciprofloxacin, levofloxacin, nalidixic acid, norfloxacin, ofloxacin
Sulfonamides: co-trimoxazole[Δ◇], sulfacetamide[Δ] (topical), sulfanilamide[Δ], sulfisoxazole, sulfamethoxazole[Δ◇], trimethoprim-sulfamethoxazole[Δ◇]
Other anti-infectives: chloramphenicol, furazolidone[Δ], isoniazid, mepacrine
Miscellaneous
Ascorbic acid (vitamin C)
Glyburide (glibenclamide)
Hydroxychloroquine[Δ] (see chloroquine)
Isosorbide dinitrate
Mesalamine (mesalazine)[Δ§]
Quinine
Succimer (dimercaptosuccinic acid)
Sulfasalazine[Δ§]
Medicines GENERALLY CONSIDERED SAFE in usual therapeutic doses in G6PD (WHO

classes II and III); NOTE: safety in WHO class I G6PD deficiency is generally not known[2]
Some agents listed are associated with nonhemolytic anemias unrelated to G6PD deficiency. For additional information, please refer to individual drug monographs.
Colchicine
Diphenhydramine
Doxorubicin
Levodopa, levodopa-carbidopa
Para-aminosalicylic acid (aminosalicylic acid)
Para-aminobenzoic acid (PABA)
Phenacetin¶
Phenylbutazone¶
ProbenecidΔ
Procainamide
Pyrimethamine
Streptomycin
SulfadiazineΔ[3]
Tripelennamine
Vitamin K, Vitamin K synthetic derivativesΔ

Please consult the G6PD deficiency favism association website for additional information on this subject: http://www.g6pd.org/en/G6PDDeficiency/SafeUnsafe/DaEvitare_ISS-it.

G6PD: glucose-6-phosphate deficiency; WHO: World Health Organization; NSAIDs: nonsteroidal anti-inflammatory drugs.
* There is marked variability in reports of drugs that are unsafe in patients with G6PD deficiency. This list is based on evidence supporting a clear association with drug-induced hemolysis. Individual characteristics (ie, degree of G6PD deficiency, dose, presence of infection) will determine actual safety or injury. Medicines known to be unsafe in G6PD deficiency that are no longer in clinical use are excluded from this list.
¶ Not available in the United States. Available in other countries.
Δ Conflicting reports. Considered unsafe for all degrees of G6PD deficiency according to some references.[3]
◇ Sulfamethoxazole may produce a modest shortening in the survival of G6PD-deficient red cells. For additional detail, please refer to UpToDate topic on clinical manifestations of glucose-6-phosphate dehydrogenase.
§ There are reports of hemolytic episodes after administration of sulfasalazine (of which mesalamine is a component) in G6PD-deficient patients as well as numerous reports of anemia with the appearance of Heinz bodies in patients who received sulfasalazine who were not G6PD deficient.

References:

1. *Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. Lancet 2008; 371:64.*
2. *Youngster I, Arcavi L, Schechmaster R. Medications and glucose6-phosphate dehydrogenase deficiency. Drug Saf 2010; 33:713.*
3. *Luzzatto L, Seneca E. G6PD deficiency: a classic example of pharmacogenetics with on-going clinical implications. Br J Haematol 2014; 164:469.*
4. *G6PD deficiency favism association website: http://www.g6pd.org/en/G6PDDeficiency/SafeUnsafe/DaEvitare_ISS-it (Accessed January 29, 2014).*

Graphic 74254 Version 16.0

Contributor Disclosures

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