During prenatal care screening tests yield a serum alpha-fetoprotein value is markedly increased.

Of the following, the MOST appropriate advice to give to this woman is that she should:

1. have an ultrasonographic examination to date her pregnancy and to search for fetal anomalies
2. have another blood sample drawn to repeat the test
3. have chorionic villus sampling as soon as possible to determine the chromosome complement of the fetus
4. obtain further testing only if she older than age 35
5. only be concerned if there is a history of open neural tube defects in her family

You selected 5, the correct answer is 1.

Alpha-fetoprotein (AFP) is produced by the fetal liver and crosses the placenta to enter the maternal circulation. Any defect that causes a breach in fetal skin can result in increased levels of AFP in the maternal circulation due to leaking of the protein. These fetal defects include open neural tube defects, anencephaly, and omphalocele. Maternal serum AFP (MSAFP) levels also can be increased in twin pregnancies, with fetal demise, and in pregnancies in which the fetus has congenital nephrosis. Because the measurement of MSAFP is simple and inexpensive, the American College of Obstetricians and Gynecologists, the American Society of Human Genetics, and the American Academy of Pediatrics recommend offering MSAFP screening to all pregnant women at 16 to 18 weeks of gestation. However, such screening should be undertaken only if there is adequate counseling, access to high-quality laboratory services, and appropriate facilities for follow-up testing (ie, qualified diagnostic centers that offer conventional and high-resolution ultrasonography and amniocentesis). More recently, additional biochemical markers have been added to this screening test to permit the identification of pregnancies at increased risk for chromosomal abnormalities, most notably trisomy 21.

Depending on the cutoff used by the laboratory to define an elevated level, which is usually 2 to 2.5 times the median value for gestational age, MSAFP screening detects most fetuses that have open neural tube defects. However, because it is a screening test, MSAFP results are abnormal in approximately 1% to 5% of pregnant women. Because the incidence of open neural tube defects is generally 1 in 1,000 or less, most findings of elevated MSAFP are due to other reasons (eg, incorrect dating of the pregnancy, other congenital anomalies, intrauterine growth retardation, multiple gestations, fetal demise). Incorrect dating is the most common reason for a falsely positive MSAFP. If the dating of the pregnancy is changed by ultrasonography, the MSAFP value should be recalculated to reassess the risk. If the dating is correct, the patient should be offered high-resolution fetal ultrasonography to search for anomalies. If ultrasonography does not provide an explanation for the abnormal result (as occurs in about 50% of cases), amniocentesis should be offered to measure amniotic fluid AFP (AFAFP).

Some laboratories request a second sample after an initial elevated MSAFP level; others proceed immediately to follow-up ultrasonography. In general, second samples should be obtained only if the initial MSAFP concentration is minimally elevated and there is sufficient time for processing a second specimen.
Clinical trials in pregnant women who have had a prior pregnancy affected by a neural tube defect have demonstrated that folic acid supplements substantially reduce the risk of recurrent neural tube defects. In one such trial, administration of 4 mg of folic acid daily beginning at least 1 month before conception through the first trimester reduced the recurrence risk of neural tube defects from 3.5% to 1.0%. Trials in women who have not had a prior affected pregnancy also have shown a beneficial effect. It is now recommended that all women of childbearing age take folic acid supplements to prevent the occurrence of neural tube defects. All women still should undergo MSAFP screening because there is no evidence to suggest that folic acid supplements can prevent all neural tube defects.

Because elevated MSAFP levels are associated primarily with open neural tube defects, which usually do not result from chromosome abnormalities, chorionic villus sampling, which is used to determine fetal karyotype, would not be indicated for the woman in the vignette. In addition, AFP cannot be measured in chorionic villi. Open neural tube defects are among the most common birth defects, occurring in approximately 1 in 1,000 pregnancies. In most cases, there is no family history, although those who do have a positive family history may be at increased risk over the general population. There is no association of neural tube defects with maternal age.

References:
Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. MMWR Morb Mortal Wkly Rep. 1992;41(RR-14):1-7

Content specification(s):
Understand the significance of abnormal maternal values on a second trimester multiscreen or alpha-fetoprotein test
A 20-year-old primigravida at 30 weeks of gestation has a blood pressure of 160/112 mm Hg, serum total bilirubin level of 44.5 mcmol/L (2.6 mg/dL), serum alanine aminotransferase level of 150 U/L, and platelet count of 75 x 10^9/L (75,000/mm^3). She is hospitalized for observation and electronic fetal heart rate monitoring.

**Of the following, the MOST ominous sign of fetal distress during monitoring would be**

- early decelerations
- increased beat-to-beat variability
- late decelerations
- spontaneous accelerations
- vitamin D deficiency

You selected __A__, the correct answer is __C__.

Hospitalization and fetal heart rate monitoring are indicated for the patient described in the vignette, who has pregnancy-induced hypertension complicated by the HELLP syndrome. This syndrome is characterized by Hemolysis, Elevated Liver enzymes, and Low Platelets and is associated with a high risk of maternal and fetal mortality.

Repetitive late **decelerations** on electronic fetal heart rate monitoring is one of the earliest signs of fetal hypoxia and acidemia. A late deceleration is a decrease in the fetal heart rate that begins after the peak of the uterine contraction. Late decelerations usually are symmetric and of low amplitude (<20 beats/min). The appearance of late decelerations is attributed to transient fetal hypoxia that occurs following a decrease in placental perfusion during the uterine contractions. The likelihood of fetal acidemia is great when the late decelerations are high amplitude and are accompanied by baseline changes in the fetal heart rate.

An early deceleration is a decrease in the fetal heart rate that begins with the onset of the uterine contraction. The fetal heart rate returns to baseline when the contraction resolves. Early decelerations are usually symmetric and of minimal amplitude (<10 beats/min). The appearance of early decelerations is attributed to an increase in vagal tone resulting from increased intracranial pressure during the uterine contractions. Early decelerations are not associated with fetal hypoxia or acidemia.

Beat-to-beat variability refers to the instantaneous changes in the fetal heart rate that occur between successive beats of the cardiac cycle. Beat-to-beat variability is influenced by the parasympathetic nervous system, and its presence is a sign of fetal well-being. Conversely, the loss of beat-to-beat variability, especially when accompanied by baseline changes in the fetal heart rate or by recurrent decelerations, is a sign of fetal hypoxia and acidemia.

Spontaneous accelerations are short-term increases in the fetal heart rate that occur independently of uterine contractions. They usually are associated with fetal movements and are seen commonly during the intrapartum period. The frequency and amplitude of spontaneous accelerations increase with gestational age.
antepartum nonstress test relies on the presence of repetitive spontaneous accelerations of sufficient amplitude and duration to assess fetal well-being.

Variable decelerations represent the most common type of fetal heart rate decelerations seen during labor. They are so named because of their variable onset and appearance in relation to the uterine contractions. The amplitude, duration, and resolution of variable decelerations differs from contraction to contraction, and their progression is unpredictable. These variable decelerations generally are not associated with fetal hypoxia or acidemia.

References:


Content Specification(s):

Understand the rationale, interpretation, and shortcomings of various methods of assessing fetal well-being during pregnancy, including fetal activity, fetal heart rate patterns, and biophysical profile

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A 29-week, 1-day gestation infant is born to a 25-year-old woman who has a history of regular menstrual periods.

Of the following, the MOST accurate term to describe the age of this infant at 5 weeks after birth is

- 34 weeks, 1 day conceptual age
- 34 weeks, 1 day fertilization age
- 34 weeks, 1 day gestational age
- 34 weeks, 1 day postconceptional age
- 34 weeks, 1 day postmenstrual age

You selected 5, the correct answer is 5.

Chronological age is the duration of time between birth and the specific day of interest. Chronological age is measured in weeks, months, and years. Postmenstrual age is determined by adding gestational age to chronological age and is the preferred term to describe the age of preterm infants through the perinatal period. Postmenstrual age typically is measured in weeks and days. Postmenstrual age differs from corrected or adjusted age. Corrected age is used most accurately to describe the age of an infant who is born preterm during the first 2 to 3 years after birth; it is calculated by subtracting the duration of time between 40 weeks and gestational age from the chronological age. For example, a 28-week gestation infant at 12 months of age has a corrected age of 9 months \(12 \text{ months} - \left(\frac{40 \text{ weeks} - 28 \text{ weeks}}{4 \text{ weeks}}\right)\). Corrected age is applied after the perinatal period has been completed.

Fertilization and implantation occur about 2 and 3 weeks, respectively, after the first day of the last menstrual period during natural pregnancies. However, when pregnancies result from the use of assisted reproductive technologies, the convention is to add 2 weeks to the number of weeks and days from implantation to determine the gestational age. This is preferred over confusing the discussion by using the terms postconceptional age, conceptional age, or fertilization age. The term conceptual age is not recommended in clinical medicine.

Gestational age is defined as the number of weeks and days between the first day of the last menstrual period and the day of delivery. This is most accurate for women who have had regular and predictable menstrual periods. For women who have irregular periods, excessive or prolonged bleeding, and breakthrough bleeding during pregnancy, this method of gestational age calculation is least accurate. Alternative methods, such as determination via prenatal ultrasonography, dates from quickening, and postnatal gestational age examination may be helpful in determining the best estimate of gestational age. In general, each of these methods of gestational age determination is accurate only to within 1 to 2 weeks.

References:

Cunningham FG, Gant NF, Gilstrap LC III, Hauth JC, Wenstrom KD, Leveno KJ, eds.


Content Specification(s):
Know when to correct for degree of prematurity when evaluating the development of preterm infants
You are called to the delivery room to care for a precipitously delivered, very depressed near-term infant. The mother's membranes ruptured 30 minutes before delivery, and she delivered shortly after arriving in the emergency department. Apgar scores were 1, 3, and 3 at 1, 5, and 10 minutes, respectively. A section of cord was double-clamped at the time of delivery, and a blood specimen was sent to the laboratory to measure cord blood gases at the request of the delivering physician. An umbilical arterial catheter was placed and another blood specimen was obtained for measurement of gases. The blood gas report was as follows:

<table>
<thead>
<tr>
<th>Site</th>
<th>pH</th>
<th>Pco2</th>
<th>Po2</th>
<th>Base Excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umbilical vein</td>
<td>7.30</td>
<td>37</td>
<td>35</td>
<td>-8</td>
</tr>
<tr>
<td>Umbilical artery</td>
<td>7.24</td>
<td>43</td>
<td>20</td>
<td>-8</td>
</tr>
<tr>
<td>Umbilical arterial catheter</td>
<td>7.03</td>
<td>25</td>
<td>130</td>
<td>-25</td>
</tr>
</tbody>
</table>

Of the following, the BEST explanation for these findings is

1. abruptio placentae
2. cord prolapse
3. fetal-maternal hemorrhage
4. uterine hypertonia
5. uterine rupture

You selected 3, the correct answer is 2.

The umbilical cord blood samples reported for the infant in the vignette are in the normal range for pH, Pco2, Po2, and base excess. It is important to remember that because the umbilical vein is delivering blood from the placenta, umbilical venous blood from the cord sample always has higher pH and Po2 and lower Pco2 than the corresponding cord umbilical arterial sample. The sample from the umbilical arterial catheter from the infant in the vignette shows severe metabolic acidosis with respiratory compensation on assisted ventilation. The cord blood gas findings are most consistent with rapid total cord occlusion, as can occur with membrane rupture and occult cord prolapse. With cord prolapse, the cord is delivering no blood to the fetus, and the blood retained in the cord vessels reflects fetal and placental status at the time of the occlusion. In partial occlusion of the cord, the venous flow is obstructed before the arterial flow, resulting in progressive asphyxia of the fetus. Umbilical venous gas measurements can be normal in the presence of abnormal arterial gas findings. Once fetal hypotension ensues, umbilical arterial perfusion fails, and the umbilical arterial gases are not affected as severely as is the fetus. Blood gases remain stable in a cross-clamped segment of cord for 60 minutes. In this vignette, fetal hypoxemia, acidosis, and depression are reflected in the clinical condition of the baby at birth and are confirmed by the gas measurements from the umbilical arterial catheter.

Fetal-maternal hemorrhage can cause severe fetal compromise and death. Placental function is unaffected, resulting in progressive disparity between the relatively
normal umbilical venous gas measurements (postplacental) and the severe metabolic acidosis represented by the umbilical arterial gas measurements. This pattern is similar to that described with umbilical venous occlusion.

In abruptio placentae, the fetal circulation is separated from that of the mother, resulting in abnormal umbilical arterial and venous blood gas values. Uterine hypertonia and uterine rupture are forms of uteroplacental insufficiency. Umbilical vessel samples in these conditions reflect severe, but relatively similar abnormalities in both the arterial and venous samples. Severe maternal anemia and significant placental dysfunction also can give similar results.

Reference:

Content Specification:
Understand the interpretation of fetal scalp and umbilical cord blood gas and pH values
You are having a discussion with the house staff on preeclampsia and its effects on the pregnancy, fetus, and newborn.

Of the following, the MOST accurate statement regarding the treatment of preeclampsia is that

1. antenatal corticosteroids are contraindicated
2. antihypertensive therapy will not improve fetal outcome
3. daily aspirin therapy can prevent preeclampsia
4. diuretics should be used to reduce peripheral edema
5. severe preeclampsia is treated by delivery only if fetal maturity can be documented

You selected 4, the correct answer is 2.

The diagnosis of preeclampsia is based on the combination of maternal hypertension and proteinuria occurring during pregnancy. Blood pressure elevation without proteinuria may evolve into preeclampsia. If no proteinuria occurs and the blood pressure is normal by 12 weeks postpartum, the diagnosis is transient hypertension of pregnancy. Persistent hypertension suggests a chronic condition. Preeclampsia usually develops in the late second trimester or third trimester of pregnancy, but presents postpartum in some cases. Although a number of pathologic findings suggest vascular, immunologic, or inflammatory factors for preeclampsia, its cause has not yet been determined.

Maternal antihypertensive therapy does not improve fetal outcome and may mask worsening hypertension. The fetal effects are due to placental changes that result in poor fetal growth (intrauterine growth retardation) and placental insufficiency. Deterioration of maternal status, eclampsia, and decreased fetal well-being are criteria for delivery. If the maternal or fetal status deteriorates, delivery is the preferred treatment option, regardless of fetal lung maturity and without delay for administration of antenatal corticosteroids.

Liver involvement indicates severe preeclampsia and should lead to maternal evaluation for the HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome. The fetal effects of preeclampsia/HELLP syndrome include preterm delivery, intrauterine growth retardation, fetal intolerance of labor, neutropenia, and thrombocytopenia. Antenatal corticosteroids may be considered if the maternal and fetal status allow delay in delivery. Corticosteroids may ameliorate the liver abnormalities and prolong pregnancy in some cases of HELLP syndrome, but as with preeclampsia, delivery is the preferred option for progressive disease. After delivery, liver function normalizes within 48 hours; thrombocytopenia resolves more slowly.

Prophylaxis for preeclampsia with aspirin and calcium has been studied, but neither has been shown unequivocally to be effective. Studies of the antioxidant vitamins C and E are ongoing, but no recommendations regarding their effectiveness have been made to date.

All hypertensive pregnant women must be monitored for proteinuria, and if preeclampsia occurs, careful maternal and fetal monitoring is mandated. Maternal effects of preeclampsia include the secondary effects of hypertension and
multiorgan effects of vasculitis. As the condition progresses, the risk of developing eclampsia (seizures) and worsening end-organ damage increases. Treatments are supportive; none is known to alter the underlying cause. Diuretics should not be administered because decreased plasma volume is a feature of preeclampsia, and reducing it further could lead to fetal compromise.

References:

Content specification(s):
Know the effects on the fetus of mild preeclampsia and its management
Know the effects on the fetus of severe preeclampsia, including HELLP syndrome, and its management
A 35-year-old woman has chronic renal disease of an undetermined cause. Her blood pressure is 132/78 mm Hg, and her glomerular filtration rate is 80 mL/min. She has a positive pregnancy test and inquires about the effects of her renal disease on the outcome of her pregnancy.

Of the following, the maternal renal disease that presents the GREATEST risk to the pregnancy is

- chronic glomerulonephritis
- periarteritis nodosa
- reflux nephropathy
- systemic lupus erythematosus
- urolithiasis

You selected 4, the correct answer is 2.

For women who have periarteritis nodosa with renal involvement, the prognosis for pregnancy is guarded largely due to the complication of malignant hypertension, which has been associated with maternal demise. In spite of some reported successful pregnancies, consideration of early therapeutic termination is recommended because of the maternal risk of death.

Among women who have acute or chronic glomerulonephritis, pregnancy is well-tolerated without adverse effects on the course of the underlying renal disease, especially when hypertension is absent and renal function is preserved (glomerular filtration rate >70 mL/min). Such women, however, must be counseled about the potential risk for aggravation of chronic disease due to the hypercoagulable state associated with pregnancy and superimposed preeclampsia or hypertensive crisis. Among women who have hypertension, renal dysfunction, or both, there is a 25% risk for de novo hypertension or superimposed preeclampsia and a 10% risk for persistent hypertension after pregnancy. These problems are more likely among women who have focal and segmental glomerulosclerosis, membranoproliferative glomerulonephritis, and immunoglobulin A nephropathy. These variants also are associated with greater risk for fetal loss.

Reflux nephropathy is associated with satisfactory pregnancy outcomes among women who have normal blood pressures and minimally affected renal function. Such women, however, must be screened for potential risks of hypertension, deterioration of renal function, and urinary tract infection.

Systemic lupus erythematosus (SLE) presents a varied pregnancy prognosis, depending on the clinical status of the disease. Among women in remission for 6 months preconception who have minimal renal dysfunction, the pregnancy outcome is favorable. Signs of disease activity or deteriorating renal function both raise the risks for pregnancy complications and the clinical course of the disease. Medications used for the treatment of SLE also may affect the prognosis. Glucocorticosteroids are associated with oral clefts in the fetus; cyclophosphamide is associated with menstrual difficulties, secondary amenorrhea, early fetal loss, and various nonspecific fetal anomalies; and azathioprine is associated with fetal growth restriction. Although there are no data in humans, animal studies suggest an
association between mycophenolate mofetil, a medication used in the treatment of SLE, and fetal resorptions and multiple anomalies. Accordingly, this drug should not be used in pregnancy. Women who have associated lupus anticoagulant may benefit from low-molecular weight heparin and aspirin treatment during pregnancy. Among women who have SLE with renal disease, approximately 25% may experience transient renal deterioration, and 8.5% may experience permanent deterioration. If the serum creatinine is greater than 1.5 mg/dL (132.6 mcmol/L), a fetal loss rate of 50% may be expected. Rarely, neonates may be afflicted with neonatal lupus erythematosus, the manifestations of which include congenital heart block, cardiomyopathy, cutaneous lesions, hepatobiliary disease, and thrombocytopenia.

Urolithiasis during pregnancy may be associated with infections that warrant antimicrobial treatment. Women who have urolithiasis should maintain adequate hydration and receive analgesics for pain as needed. Most renal stones, such as calcium oxalate or calcium brushite, are benign, but occasionally struvite (infected or staghorn) stones require specialized management, including lithotripsy. Cystine stones associated with cystinuria require high fluid intake, with D-penicillamine administration reserved for situations associated with extremely high urinary cystine levels.

References:


Content specification:

Know the effects on the fetus of acute and chronic renal disease and their treatment
A 41-year-old woman, who has been married to the same man for 22 years and has two living healthy children (ages 10 and 16 y), has experienced two first-trimester fetal losses in the past 6 years. She now presents with a positive pregnancy test at an estimated gestational age of 7 weeks. She takes no medications except for a daily dose of levothyroxine. She smokes one to five cigarettes per day, has one cup of coffee each morning, and takes one or two alcoholic drinks during weekends. She reports that one of her living children was treated for chlamydial infection in the neonatal period.

Of the following, the feature in the history of this woman that has the STRONGEST relationship with repeated first-trimester fetal losses is

- caffeine consumption
- chlamydial infection
- maternal age
- tobacco smoking
- thyroid supplementation

You selected 3, the correct answer is 3.

Spontaneous fetal losses are more likely with advancing maternal age, and approximately 80% of such losses occur in the first trimester. Women younger than 20 years of age have a 12% risk of first-trimester fetal loss, which increases to 26% among women older than 40 years of age. Advancing paternal age also increases the risk. Chromosomal abnormalities are present in about 50% of first-trimester fetal losses. When analyzed for the origin of the abnormal gametogenesis, errors in maternal gametogenesis are identified in 25% and errors in paternal gametogenesis in 5% of the cases. The most frequent chromosomal error among first-trimester fetal losses is autosomal trisomy. Trisomy of every autosome, except chromosome 1, has been reported, with chromosomes 13, 16, 18, 21, or 22 being the most prevalent. The extra chromosome in trisomy is maternal in origin in most of the cases. Balanced chromosomal rearrangements account for 2% to 3% of couples who experience repeated losses. Triploidy is found among women whose pregnancies are complicated by the development of an incomplete hydatidiform mole. In contrast to the other chromosomal abnormalities, the incidence of triploidy is not age-related. When fetal aneuploidy is present, the mean gestational age at the time of the fetal loss is 8 weeks. The fetal loss occurs at a mean gestational age of 13 weeks under the condition of euploidy.

Although caffeine consumption exceeding four cups of coffee per day has been associated with pregnancy loss, moderate use of caffeine, as described for the woman in the vignette, has no such association.

Maternal infection with Chlamydia has been associated with fetal loss in animals, but not documented in humans. Maternal infections associated with fetal loss in humans include herpes simplex virus, human immunodeficiency virus-1, and syphilis. The association between maternal infection with Toxoplasma gondii and fetal loss among humans is inconclusive. Although Brucella abortus, Campylobacter fetus, and Listeria monocytogenes have been implicated in animal studies, none has been related to fetal loss among humans.
Tobacco smoking is associated with an increased risk for fetal loss, with an estimated increase by a factor of 1.2 for every 10 cigarettes smoked per day. In addition to the risk of fetal loss, smoking in pregnancy increases the risk for fetal undernutrition and preterm delivery. Maternal smoking also has been associated with an increased risk for sudden infant death syndrome. Maternal alcohol consumption increases the risk of spontaneous fetal loss by a factor of 1.3 for each drink per day. The smoking by the woman described in the vignette is below the threshold of 10 cigarettes per day, and her alcohol consumption is minimal.

Maternal hypothyroidism commonly is associated with infertility. The occasional affected woman who becomes pregnant has increased risks of preeclampsia, placental abruption, and fetal undergrowth and stillbirth. First-trimester fetal losses are unusual. The maternal levothyroxine treatment described for the woman in the vignette does not increase her risk of first-trimester fetal loss.

Reference:


Content Specification(s):

1542. Know the causes and assessment of spontaneous first trimester loss
Cesarean delivery of 33-week twins, both male, is necessary due to severe preeclampsia unresponsive to treatment since presenting four hours ago. The mother was a fraternal, or dizygotic, twin. She conceived the month after stopping oral contraceptive therapy. Sonographic evaluation shows dichorionic, diamniotic twins with discordant growth. Twin A is estimated to weigh 1750 grams and twin B to weigh 1125 grams. Hydramnios has been present since 18 weeks in Twin B. While preparing for resuscitation and stabilization of these infants, you are discussing information about twin gestations with the pediatric residents and nurse practitioners.

Of the following, the TRUE statement regarding twinning is:

1. dichorionic, diamniotic placentas indicate that the twins are dizygotic
2. malformations occur more frequently in twin pregnancies complicated by transient hydramnios during the second trimester
3. monozygotic twins are phenotypically identical
4. most twins deliver at term
5. women who themselves are dizygotic twins have a greater chance for having dizygotic twins than fathers who themselves are dizygotic twins

You selected 5, the correct answer is 5.

Twin pregnancies account for the majority of multifetal pregnancies. In the United States, the number of twin births has increased by more than 50% between 1980 and 1997, whereas singleton births rose by 6%. This disproportionate increase has been attributed to an increase in pregnancies achieved with artificial reproductive therapy. Twins account for approximately 1 in 94 naturally occurring pregnancies. However, they also account for a large share of fetal, neonatal and maternal pregnancy complications. Fetal and neonatal complications include higher rates of perinatal mortality, congenital malformations and twin-twin transfusion syndrome. Maternal complications include a two-fold risk of preeclampsia, postpartum hemorrhage and maternal death.

Twin gestations result from fertilization of two separate ova (dizygotic or fraternal) or from a single fertilized ovum that divides into two structures capable of developing into separate individuals (monozygotic or identical). Dizygotic twins result from fertilization of two ova during the same ovulatory cycle, i.e., they are two separate offspring who share the same time and place in which to develop into two individuals. Dizygotic twins account for approximately two-thirds of all twins, monozygotic twins for about one-third.

Dizygotic twinning is determined in part by the family history. Mothers who themselves are dizygotic twins have a 1 in 58 chance of a twin conceptus; this is a two-fold greater chance than fathers who themselves are dizygotic twins. This has been hypothesized to be due to an autosomal dominant gene that increases the number of follicles that can produce ovum for fertilization by prolonging the effect of follicle stimulating hormone (FSH). The mechanism may be an increase in synthesis and release of FSH or increased receptor sensitivity to FSH, or both. This same mechanism also may account for the increased chance of twinning soon after discontinuing oral contraceptives, when a rebound release of endogenous pituitary gonadotropin occurs. The influence of race, age, weight and fertility also may be due to prolonged FSH effect. Research is ongoing to test this hypothesis.

Dichorionic, diamniotic placentas may indicate either monozygotic or dizygotic twins.
Monochorionic or monoamnionic placentas indicate monozygosity. However, dichorionic, diamniotic placental structures also occur in monozygotic twins if division of the fertilized ovum occurs before the inner cell mass (morula) is formed and the outer layer of the blastocyst is committed to chorion development. This usually occurs within 72 hours of fertilization. In contrast, a diamniotic, monochorionic twin pregnancy will occur if division of the developing morula and chorion occurs between four and eight days after fertilization. This occurs when the inner cell mass and chorionic structures are committed but amniotic differentiation has not committed so that two amniotic sacs form. Monoamniotic, monochorionic placentas develop when the inner cell mass, chorionic structures and amniotic structures have committed to a direction of differentiation before division occurs; this happens eight days or more after fertilization. In rare instances when division occurs even later, after the embryonic disk is formed, conjoined twins result, because separation is nearly always incomplete.

Monzygotic twins may or may not be phenotypically identical. This is dependent on the amount of tissue that accompanies division of the fertilized ovum. Differences in tissue allocation during division can result in discordant growth and development. The discordant growth of the twins in the vignette raises suspicion for monozygosity and associated complications of cord entanglement, congenital anomalies and twin-twin transfusion syndrome. Discordancy for genetic mutations or gene expression and, in female fetuses, different patterns of lyonization, can produce different phenotypes in monozygotic twins. Congenital malformations are particularly more common in monozygotic twins compared to singletons; major malformations occur in 2% and minor malformations in 4% of twins. These anomalies result from defects during the twinning process itself (eg, conjoined twins, neural-tube defects, sirenomelia, holoprosencephaly), vascular accidents due to interchange of blood flow and emboli through vascular anastomoses (eg, microcephaly, hydranencephaly, intestinal atresia, aplasia cutis or limb amputation) or deformations due to crowding (eg, talipes equinovarus, hip dislocation). One clinical clue to the presence of malformations is the presence of hydramnios persisting throughout pregnancy. Both twins in the vignette should be evaluated for congenital malformations, especially twin B, whose course has been complicated by hydramnios.

Twin gestations account for about 12% of all spontaneous conceptions, but only approximately 14% of these survive to term. A greater risk of spontaneous abortion occurs with twins, especially if monochorionic. Interestingly, in some twin pregnancies, one of the twins is lost before the second trimester; this is referred to as the "vanishing twin" and occurs in 21% to 63% of spontaneous twin pregnancies. At the time of delivery, there is usually no evidence of the lost fetus.

References:


Content Specification:

Understand the implications and complications of multiple gestation, such as cord problems, twin-twin transfusion, "stuck twin," conjoined twins, etc.
A female infant of 35 weeks’ gestation is admitted to the neonatal intensive care unit for mild respiratory distress and temperature instability. Her mother is a 23-year-old woman with no medical illnesses, and this is her first pregnancy. Family history is remarkable for seizures in a cousin, neurofibromatosis in an uncle, and hypertension in both sets of grandparents.

The mother's menstrual cycles have been regular every 28 days until she became pregnant. A small amount of vaginal bleeding was noted 3 weeks after her last normal menstrual period. Prenatal care began at 9 weeks' gestation, dated from the first day of her last menstrual period. Sonography at that time was consistent with a gestational age of 9 weeks. Subsequent sonographs at 20 and 28 weeks' gestation were consistent with dates and normal fetal growth.

Fetal heart tones were heard at 13 weeks' gestation using Doppler technology. Fundal height estimation of gestational age had been consistently 2 weeks behind that, based on the first day of the last menstrual period. Physical examination after birth is remarkable for tachypnea, nasal flaring, and minimal subcostal retractions. The infant's temperature is 35.6° C on admission. Oxygen saturation by pulse oximetry is 96%. Her Ballard score is consistent with a gestational age of 33 weeks.

Of the following, the MOST accurate measure of gestational age is:

1. embryonic crown-rump length at 9 weeks' gestation
2. fetal heart tones using Doppler technology
3. fundal height measurements
4. gestational sac diameter measurement at 5 weeks' gestation
5. postnatal Ballard score

You selected 2, the correct answer is 1.

Gestational age assessment is a fundamental determination for physicians caring for pregnant women, children, and their families. Knowledge of gestational age is an indicator of neonatal maturity and associated morbidity and mortality. Clinical interventions and management strategies often can be anticipated when the gestational age is known. For example, an infant assessed to be 26 weeks' gestation at birth can be anticipated to have some respiratory distress and, perhaps, would benefit from surfactant replacement. Indeed, from a public health perspective, gestational age at birth and birthweight are indicators of the population's fetal and neonatal health.

Gestational age generally is based on the first day of the last normal menstrual period. This estimation is the gold standard when the menstrual cycle length is regular and occurs approximately every 28 days. If the duration of the menstrual period is shorter or longer than usual, as occurs in some women with variable durations of preovulatory and blastocyst implantation phases of the menstrual cycle, the last menstrual period may inaccurately reflect gestational age. Maternal recall error about the first day of the last normal menstrual period, implantation bleeding several weeks into the pregnancy (as seen in the mother in this vignette), and preconception amenorrhea after oral contraceptive use add to the variability in gestational age assessment. Because of this variability, more accurate methods of determining gestational age continue to be investigated.

In the absence of reliable menstrual dates, the most accurate assessment of gestational age is with sonographic measurement of the embryonic crown-rump length. When performed between
5 and 12 weeks' gestation, as in this vignette, dating is accurate to +3 days. In contrast, gestational sac diameter measurement performed sonographically at about 5 weeks' gestation is accurate to within 5 days.

Sonographic measurement of the triad of biparietal diameter, femur length, and cerebellar transverse diameter are accurate to within 10 days and 14 days at 15 to 22 weeks' gestation and >22 weeks' gestation, respectively.

Maternal physical measures of fundal height and Doppler detection of fetal heart tones are accurate to only +2 to 3 weeks. Postnatal physical examination using the Ballard scale is accurate to +2 weeks if the infant is born >28 weeks' gestation and +3 weeks if the infant is born <28 weeks' gestation.

References:


Content Specification:

Know the ultrasound findings and their limitations in determining gestational age
A pregnant woman is involved in a motor vehicle accident that causes blunt trauma to her abdomen. As you await evaluation by the emergency physicians and obstetricians, you discuss the potential risk to the fetus with colleagues and medical students.

Of the following, the MOST accurate statement regarding fetal risk in motor vehicle accidents is that:

1. absence of vaginal bleeding is reassuring regarding placental abruption
2. fetal death often occurs with maternal survival
3. fetal risk is proportional to gestational age
4. maternal trauma score predicts pregnancy risk
5. monitoring of the fetus for 24 hours is mandated

You selected 4, the correct answer is 3.

Fetal risk increases with gestational age because of the protective effect during the first trimester of the intrapelvic location of the uterus early in pregnancy, the fluid in the amniotic sac, and the pelvic soft tissues. However, severe pelvic fractures may result in fetal loss in early gestation. Except for situations of maternal death from motor vehicle accidents, first trimester fetal loss rarely is explained by trauma. After 12 weeks' gestation, as the uterus ascends above the pelvis, the uterus and fetus become more vulnerable to blunt trauma or penetrating injuries. The risk to the mother and fetus are proportional to the degree of damage to the vehicle. Injury to the fetus may be direct, such as skull fracture or hemorrhage, or indirect as a result of disruption of uteroplacental exchange, such as placental abruption or uterine rupture.

Placental abruption may follow abdominal trauma and should be considered in all cases. Fetal monitoring for uterine contractions and fetal heart rate (FHR) abnormalities, marking and monitoring of the uterine fundal position, and evaluation for uterine tenderness are recommended. Although vaginal bleeding may accompany placental abruption, its absence is not reassuring. In a series of 16 cases of placental abruption resulting in fetal death, only 6 were associated with vaginal bleeding.

Fetal death from motor vehicle accidents after 12 weeks' gestation most often is the result of maternal death. Placental abruption and uterine rupture are the most common causes of fetal demise in cases of maternal survival. In one report of pregnant women in severe accidents, abruption occurred only in 3.4%.

As in nonpregnant patients, trauma severity scoring such as the Glasgow Coma Scale is useful in triaging the mother, but the scores are not predictive of pregnancy outcome.

Fetal monitoring is useful after abdominal trauma. Obstetric ultrasonography can help to determine gestational age, placental location, and fetal position. FHR is a proxy for fetal well-being, adequacy of maternal blood volume, and compensatory alpha-adrenergic response. Fetal bradycardia (<120 beats/min) or late decelerations may reflect maternal hypovolemia, maternal hypoxia, abruption, or uterine rupture. If the mother has been resuscitated and is stable after a major trauma, cesarean delivery should be considered if fetal distress is present. Monitoring for 4 to 8 hours is recommended for pregnant women involved in motor vehicle accidents even if there is no history of abdominal impact. With fewer than six contractions per hour and no FHR abnormalities, monitoring can be discontinued. If contractions occur more frequently than every
10 minutes, the risk of abruption is 20%. If there are frequent uterine contractions or fetal heart abnormalities, monitoring should be extended to at least 24 hours unless fetal compromise or maternal deterioration dictates urgent delivery. Relatively minor abdominal trauma may result in fetal-maternal hemorrhage. A Kleihauer-Betke test and measurement of maternal serum alpha-fetoprotein may be used to estimate the presence and volume of fetal-maternal hemorrhage. Only a tiny amount of Rh(+) blood is needed to sensitize the Rh(-) mother. Rh(-) women should receive Rh immunoglobulin G (RhIgG). Larger doses of RhIgG and ongoing fetal surveillance may be indicated if more than 30 mL of fetal blood is detected in the mother.

References:

Mackenzie S. Obstetrics: trauma and pregnancy.

Newton ER. EMedicine-Trauma and pregnancy.

Content specifications:
Know the maternal and fetal risks and the management of a pregnant patient involved in a traumatic injury
You are asked to consult with a woman who is 26 weeks' pregnant with twin male fetuses. The prenatal ultrasound fails to demonstrate a dividing membrane between the twins.

Of the following, the complication of twin pregnancy MOST likely to develop in this woman is

1. acardiac twinning
2. conjoined twins
3. twin-to-twin transfusion
4. umbilical cord entanglement
5. vanishing twin syndrome

You selected 2, the correct answer is 1.

Absence of a dividing membrane, as described in the vignette, confirms that this woman is pregnant with monozygotic twins with monoamniotic placentation. Monozygotic twins may have three different types of placentation: diamniotic/dichorionic (Figure 1), diamniotic/monochorionic (Figure 2), or monoamniotic/monochorionic (Figure 3). Monoamniotic/monochorionic placentation, the rarest type, occurring in <1% of monozygotic twins, has the highest rate of complications.

Umbilical cord entanglement (Figure 4) is the most likely because there is no amniotic membrane separating the fetuses. Fetal mortality rate in monoamniotic twins is approximately 40%, primarily due to umbilical cord entanglement with subsequent vessel occlusion. True knots in the umbilical cord have been diagnosed as early as 10 weeks' gestation. Although fetal demise from cord entanglement and occlusion can happen throughout gestation, the incidence is highest during early pregnancy, when space between the twins is greatest and more fetal movement occurs. Intensive fetal surveillance of monoamniotic twins should occur from the period of fetal viability until delivery. Because entangled umbilical cords can tighten during labor, cesarean delivery may be considered.

Acardiac twinning, known also as twin reversed arterial perfusion (TRAP) sequence, is a rare complication of monozygotic twins. Acardiac twinning occurs when one monozygotic twin has an absent or rudimentary heart and is usually acephalic. The incidence of acardiac twinning is 1% of monochorionic twins or 1 in 35,000 live births. The cause of acardiac twinning is early development of an arterial-to-arterial anastomosis between the umbilical arteries of twins. The normal donor (pump) twin provides circulation for itself and the recipient (perfused) twin through umbilical artery to umbilical artery anastomosis at the placental surface. The term "reversed perfusion" is used because blood enters the acardiac twin through the umbilical artery and exits through the umbilical vein. Cardiac failure can occur in the donor twin because of excessive demands from the TRAP sequence, especially if the acardiac twin is larger than the pump twin. The diagnosis of acardiac twins is made by fetal ultrasound.

Conjoined twins, which occur in approximately 1 in 50,000 live births, are the result of incomplete division of monozygotic twins 13 to 15 days after conception. Conjoined twins always have monoamniotic placentation. Conjoined twins are classified based on the site of attachment into five types: thoracopagus (75% of conjoined twins), pygopagus (20%), ischiopagus (5%), craniopagus (<1%) and omphalopagus (<1%). Prenatal diagnosis usually is made by an ultrasound that reveals conjoined fetuses in a single sac.

Twin-to-twin transfusion syndrome is a complication of monochorionic placentation in which
arterial-to-venous shunts develop in the placenta and preferential blood flow occurs from one twin to the other. Vascular communications are present in almost all monochorionic placentas; clinically significant twin-to-twin transfusion occurs in <5% of monochorionic gestations. Because all monoamniotic twins also have monochorionic placentas, the twins described in the vignette are at risk to develop twin-to-twin transfusion. However, the likelihood of umbilical cord entanglement is greater than twin-to-twin transfusion syndrome in monoamniotic twins.

The vanishing twin syndrome occurs with the identification of a multifetal gestation with subsequent demise and disappearance of one (or more) fetus(es). The frequency of the vanishing twin syndrome is difficult to ascertain because it usually occurs early in pregnancy. Vanishing twin syndrome has been diagnosed more frequently since the use of ultrasound in the first trimester. In vitro fertilization techniques have improved the understanding of vanishing twin syndrome because these pregnancies are monitored, and the number of implanted fertilized eggs is known.

In vanishing twin syndrome, there may be complete reabsorption of a fetus, formation of a fetus papyraceus (ie, a "mummified" or compressed fetus), or development of a subtle abnormality on the placenta, such as a cyst, subchorionic fibrin, or amorphous material.

The fetal loss is usually asymptomatic for the pregnant woman, but may be associated with modest vaginal bleeding. It is estimated that 5% of pregnant women who have first-trimester vaginal bleeding are experiencing a vanishing twin. Because the woman in the vignette is 26 weeks' pregnant, a fetal demise with subsequent reabsorption makes vanishing twin syndrome unlikely.

References:


Content Specifications:
Know the types of and effects on the mother of multiple gestation pregnancy
Know the morphologic development of the placenta
Figure 2. Diamniotic/monochorionic placenta.
Figure 4

Figure 4. Umbilical cord entanglement in monoamniotic twins.
You are asked to resuscitate a 24-weeks' gestation male infant in the delivery room. He was born preterm despite maternal treatment with magnesium sulfate for severe pregnancy-induced hypertension. Maternal serum magnesium concentration is 6.5 mg/dL (2.7 mmol/L). His mother was given betamethasone 48 hours before delivering vaginally.

Of the following, the intervention MOST likely to be needed to stabilize this infant is

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<tr>
<td></td>
<td>bag-mask ventilation</td>
<td>chest compressions</td>
<td>continuous positive airway pressure</td>
<td>surfactant</td>
<td>tactile stimulation</td>
<td></td>
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</tbody>
</table>

You selected 2, the correct answer is 1.

Bag-mask ventilation of the lungs is the most likely intervention required to stabilize the extremely low birthweight infant in the vignette. Ventilation of the lungs is the most important intervention during neonatal resuscitation, because respiratory distress and apnea are the most frequent reasons for cardiopulmonary decompensation after birth. This observation is especially true in this extremely low birthweight infant, who likely will have apnea due to hypermagnesemia. Maternal and neonatal magnesium concentrations often are similar, because magnesium readily crosses the placenta. Other neonatal complications of hypermagnesemia include hypotonia, ileus, delayed passage of meconium, and, after prolonged fetal exposure, meconium obstruction.

Chest compressions usually are not required in neonates who need resuscitation. Initiation of ventilation is associated most often with a rapid rise in heart rate. This improvement in heart rate may be followed by improved color, tone, and spontaneous respiratory efforts. In the extremely low birthweight infant in this vignette, apnea may persist for hours. After initial stabilization of vital signs with bag-mask ventilation, mechanical ventilation likely will be needed.

Continuous positive airway pressure (CPAP) is an alternative respiratory support strategy in infants who are breathing spontaneously with acceptable vital signs. In the infant in this vignette, apnea associated with extreme prematurity and hypermagnesemia is likely. Therefore, a period of positive pressure ventilation before spontaneous breathing occurs should be anticipated. In addition, the delivery room use of CPAP to provide respiratory support after initial resuscitation steps has been suggested in large case series to reduce the need for mechanical ventilation in the delivery room, bronchopulmonary dysplasia, and other complications of prematurity. Although more than half of infants less than 28 weeks’ gestation may not require intubation and mechanical ventilation in the delivery room, within the first days after birth, 80% will require mechanical ventilation. Whether a delay in initiation of mechanical ventilation with delivery room CPAP is safe and effective compared to delivery room intubation and positive pressure ventilation is unknown. Randomized clinical trials to answer this question are in progress.

Surfactant administration in this infant likely will be needed, because more than 80% of infants born at 24 weeks’ gestation receive surfactant within hours of birth. Surfactant administration before the first breath was hypothesized to improve dispersion of surfactant throughout the lung. It does not appear that outcomes are different if extremely preterm infants receive
surfactant before the first breath or after initial resuscitation and stabilization. Therefore, a commonly accepted practice is to initiate and support breathing first, then administer surfactant if a surfactant deficiency is evident.

Tactile stimulation is one of the initial steps in resuscitation of newborn infants. Extreme prematurity and hypermagnesemia-associated apnea make it likely that positive pressure ventilation will be required. After initial brief tactile stimulation with drying and positioning, positive pressure should be initiated with a bag and mask. Prolonged attempts at tactile stimulation probably will not be effective in the infant in this vignette and may be associated with injury to the skin.

References:


Content Specifications:

Understand the proper approach to airway management in the delivery room

Know the indications for assisted ventilation in the delivery room

Understand the indications, techniques and potential complications of chest compression
On a television news magazine program, a female business student declared, "I plan to be super fit, super in shape when I'm 40, 50. And if I'm physically able to do it, then I will have a child at 55." The number of first births (per 1,000 women) at ages 35 to 39 increased by 36% in the decade 1991 through 2001, with 263 births reported among women 50 to 54 years of age. You are preparing a presentation on the implications of delayed childbearing on perinatal outcomes.

Of the following, the MOST accurate statement regarding delayed childbearing is that

1. fertility declines linearly from menarche to menopause
2. hypertensive complications decrease with advancing maternal age
3. in vitro fertilization with donor eggs reduces fetal risk of aneuploidy among older women
4. paternal age is a major influence on miscarriage rates among older women
5. stillbirth rates remain stable over the childbearing years

You selected 5, the correct answer is 3.

As the combination of careers, available reproductive options, and control over health outcomes becomes an increasingly powerful influence on childbearing, more women are exploring the potential for delayed motherhood. Using techniques of in vitro fertilization with eggs donated by women in their 20s or 30s, many women in their 40s and 50s can become pregnant. Once pregnancy is established, the risks of miscarriage and chromosomal abnormalities are consistent with the age of the donor. Studies on human trisomies regardless of the chromosome involved have found them to originate with errors in maternal meiosis I (separation of homologous chromosomes). Because meiosis I is initiated in the fetal ovary and is completed at ovulation many years later, age-related influences on the meiotic process (degradations of meiotic proteins) are more influential with advanced maternal age. Thus, older women who undergo in vitro fertilization with younger eggs have a reduced risk of fetal aneuploidy.

Among women trying to conceive, the rate of childbearing is stable at greater than 400 pregnancies per 1,000 women per year until about 30 years of age. Thereafter, the rate decreases rapidly and nonlinearly, reaching fewer than 50 pregnancies per 1,000 women older than 45 years of age. Advanced maternal age is associated with deterioration in the quality of ova, which results in both reduced fertility and increased chromosomal abnormalities.

Women in their 40s experience twice the rate of hypertensive complications of pregnancy compared with younger women. These complications contribute to the increased risk of delivering a small-for-gestational age or preterm infant noted among women older than 40 years of age.

Advanced paternal age is associated with an increased risk for autosomal dominant conditions such as achondroplasia and Marfan syndrome due to new genetic mutations, but it is not a major influence on maternal miscarriage rate. Miscarriage is a major contributor to the progressive decline in fertility with age, rising from a rate of 10% at 20 years of age to more than 90% among women older than 45 years of age. Karyotyping after miscarriage demonstrates a chromosomal abnormality in two thirds of pregnancies lost before 20 weeks’ gestation.

Stillbirth, fetal death after 20 weeks of pregnancy, increases from 4 per 1,000 pregnancies among women in their 20s to 10 per 1,000 pregnancies among women older than 40 years of age. Although uncommon, the stillbirth rate is approximately 10 times the risk of sudden infant death.
death syndrome.

References:

Content Specification(s):
Understand organ and integrated physiology of maternal adaptation to pregnancy and know the normal changes in physiologic variables and in laboratory values.
You are asked to determine whether preterm twin males who have identical blood types are monozygotic or dizygotic twins. You request the pathology report on the placenta.

Of the following, the MOST common type of placentation in monozygotic twins is

1. dichorionic/diamniotic with a single placenta
2. dichorionic/diamniotic with two fused placentas
3. dichorionic/monoamniotic with two separate placentas
4. monochorionic/diamniotic with a single placenta
5. monochorionic/monoamniotic with a single placenta

You selected 3, the correct answer is 1.

Determining whether twins are monozygotic or dizygotic is important for social and medical reasons. Family members have a keen interest in whether their twins are identical or fraternal. The medical reason to determine zygosity is because monozygotic twins are the perfect match if a future organ or bone marrow transplant is needed. Examining the placenta and fetal membranes determines zygosity in approximately 20% of twin pairs.

The placenta has fetal and maternal components. The fetal portion develops from the chorionic sac. The maternal portion is derived from the endometrium. The chorion is the outer fetal membrane that appears thick and opaque. The amnion is the inner fetal membrane that appears thin and nearly transparent.

Monozygotic twins are the result of a single fertilized ovum splitting during the first 2 weeks after conception. The timing of the split results in different types of placentation. The most common (70%) form of placentation in monozygotic twins is monochorionic/diamniotic, which occurs when the fertilized ovum splits between 3 and 8 days after fertilization (Fig. 1). Monochorionic twin placentas may contain vascular anastomoses that can result in twin-twin transfusion syndrome.

Dichorionic/diamniotic placentas represent the second most common form of placentation in monozygotic twins, occurring in 30% of monozygotic twins and nearly 100% of dizygotic twins. Twins that have dichorionic/diamniotic placentas always have two separate placentas that either can be separate (Fig. 2) or fused (Fig. 3). Dichorionic/diamniotic placentas occur in monozygotic twins when the zygote splits between 1 and 3 days after fertilization.

Because the amniotic cavity develops within the chorion, dichorionic/monoamniotic placentation cannot occur.

Monochorionic/monoamniotic with a single placenta is a rare form of placentation that occurs in 1% of monozygotic twins (Fig. 4). A monochorionic/monoamniotic placenta develops when the zygote splits between days 9 and 12 after fertilization. Twins that have monochorionic/monoamniotic placentation are at the highest risk for fetal demise because umbilical cords can become entangled without a separating membrane. If twinning occurs beyond 12 days after fertilization, the monozygotic pair splits only partially, which results in conjoined twins. Conjoined twins always have monochorionic/monoamniotic placation.

When two sperms fertilize two ova, dizygotic twins result. Dizygotic twins nearly always have dichorionic/diamniotic placentation. There is a case report of monochorionic/diamniotic dizygotic twins conceived by in vitro fertilization. Dichorionic/diamniotic placentas may fuse if...
implantation sites are proximate. Fused placentas can be separated easily after birth.

References:


Content Specification(s):

Know the types of and effects on the mother of multiple gestation pregnancy
Know the morphologic development of the placenta
One year after delivering her second infant by cesarean delivery because of placenta previa, a woman becomes pregnant for the third time. Her first child was delivered vaginally at term. She expresses an interest in delivering this third infant vaginally and inquires about the pregnancy outcomes of vaginal birth after cesarean (VBAC) section for mothers and infants.

Of the following, the MOST accurate statement regarding VBAC is that

1. augmentation of labor produces a rate of uterine rupture similar to that following spontaneous onset of labor
2. increasing numbers of mothers previously delivered by cesarean section are delivering vaginally
3. neonates delivered by VBAC incur a lower risk of stillbirth, neonatal death, or hypoxic-ischemic encephalopathy
4. successful vaginal delivery in the past improves the potential for successful VBAC
5. uterine rupture during a trial of labor occurs only in the presence of a classic uterine incision

You selected 5, the correct answer is 1.

Cesarean births now occur in about 26% of pregnancies, up from 4% in 1950 and 5% in 1970. Noting that 98% of women who delivered by cesarean section subsequently delivered by repeat cesarean section, goals were set in the 1980s to encourage VBAC and to reach a VBAC rate of 35% by the year 2000. By 1996, the rate had reached 28.6%. Due to reports of higher perinatal mortality and increased numbers of uterine rupture associated with trials of labor, the VBAC rate decreased to 12.6% by 2002. Overall, VBAC is associated with more perinatal risk (odds ratio [OR], 1.96; 95% confidence intervals [CI], 1.73 to 2.22) than elective repeat cesarean delivery, but statistical analyses reveal that approximately 588 elective cesarean deliveries are needed to avert each severe adverse perinatal outcome. Some mothers and physicians consider this risk acceptable to attempt vaginal delivery; others do not.

Detailed outcomes of VBAC were reviewed from 19 academic medical center hospitals involved in a study of VBAC from 1999 through 2002. These centers followed the guidelines of the American College of Obstetricians and Gynecologists that required immediate availability of emergency cesarean section during trials of labor in women attempting VBAC. Among the factors associated with successful VBAC were previous vaginal delivery and previous VBAC. Mothers who had smaller infants were more likely to undergo a trial of labor after cesarean section.

The overall risk for uterine rupture among women undergoing a trial of labor was about 5 to 7 per 1,000 deliveries. After previous cesarean section, women who entered labor spontaneously had less chance of uterine rupture than did women whose labor either was induced (OR, 2.86; CI, 1.75 to 4.67) or augmented with oxytocin, prostaglandins, or both (OR, 2.42; CI, 1.49 to 3.93). Women delivered by elective cesarean section without labor evidenced uterine rupture in 1.6 per 1,000 deliveries in one study, and "uterine dehiscence" was described among 0.5% of 15,000 women delivering by elective cesarean section in a second study. Although data regarding maternal complications have been inconsistent, the most recent analysis by Landon and associates found elective cesarean section to be associated with a lower rate of endometritis and blood transfusion, with no difference in needs for hysterectomy or in maternal death.

Overall, a trial of labor presents a greater chance (OR, 1.95; CI, 1.73 to 2.22) for adverse maternal events than does elective repeat cesarean section.

As noted previously, after a peak VBAC rate of 28% in 1996, the rate dropped to 12.6% in 2002, resulting in fewer women delivering by VBAC in recent years. Due to the declining rate of trial of labor during the projected 3-year study period for the previously cited multicenter study, an
additional year was added to obtain sufficient data to analyze perinatal outcomes associated with VBAC.

The risk to the infant for stillbirth, neonatal death, or hypoxic-ischemic encephalopathy (HIE) was significantly greater (OR, 2.72; CI, 1.49 to 4.97) among infants whose mothers underwent a trial of labor. Of 12 cases of HIE, 6 followed spontaneous onset of labor, 2 followed augmentation, and 4 followed induction of labor. Seven of the 12 were associated with uterine rupture, and two of the 12 infants died in the neonatal period. The incidence of neonatal death from uterine rupture was 0.1 to 0.4 deaths per 1,000 trials of labor. The overall perinatal mortality rate among women undergoing trials of labor was 4 per 10,000 deliveries contrasted to 1.4 per 10,000 deliveries among women undergoing elective cesarean section delivery in the multicenter trial.

The risk for uterine rupture during the trial of labor was 0.7% if the previous cesarean section was performed via a low transverse uterine incision. A low vertical incision was associated with a 2% risk, and classic, inverted T, or J incision types were associated with a 1.9% risk in the series by Landon and associates. The incidence of uterine rupture was 4% to 9% with classic or T-shaped incisions, 1% to 7% with low vertical incisions, and 0.2% to 1.5% with low transverse incisions.

References:


Content Specifications:

Know the indications for cesarean delivery

Know the maternal and fetal/newborn complications of cesarean delivery

Know the advantages of, indications for, and complications of vaginal delivery
Public health personnel report a recent upsurge in syphilis in your community. Healthcare colleagues ask you about the risks of transmission to infants, the signs of disease in newborns, and the impact of the disease on perinatal health.

Of the following, the MOST accurate statement regarding maternal-fetal transmission of *Treponema pallidum* is:

1. Fetal risk is greatest early in pregnancy.
2. Infants with disease will be symptomatic at birth.
3. Most women with syphilis will have unaffected newborns.
4. Risk of fetal infection is most affected by maternal stage of syphilis.
5. Transmission most often occurs by contact with genital tract lesions during birth.

You selected 5, the correct answer is 1.

The incidence of syphilis in the United States declined progressively until the early 2000s, with some rise thereafter, mostly due to disease among homosexual males. The incidence among women decreased. National surveillance data for congenital syphilis (CS) show a progressive decrease in rate from 14.2 cases per 100,000 live births in 2000 to 11.2 cases per 100,000 live births in 2002. All nonwhite racial and ethnic populations shared in this decrease, while the rate among nonHispanic white infants remained constant. Geographically, the rate increased by 0.9% in the northeast United States, while it decreased by 12.5% to 29.5% in other areas of the country.

Among CS cases evaluated in 2002, 73.8% were associated with lack of or inadequate maternal treatment, 14% with treatment followed by an inadequate serologic response and inadequate infant evaluation, and 8.6% with an inadequate maternal serologic response to treatment with clinical or laboratory evidence of CS in the infant.

Fetal risk is most affected by the stage of disease in the mother. Primary syphilis manifests as a painless papule at the inoculation site, which ulcerates to produce a chancre. Although the chancre heals within three to six weeks, widespread dissemination occurs. Secondary syphilis manifests in about 25% of untreated patients in a wide variety of symptoms: a systemic papular rash involving trunk, extremities, palms and soles; lymphadenopathy; alopecia; and nonspecific neurologic manifestations. Similar to primary syphilis, these manifestations resolve, even in untreated individuals. Latent syphilis refers to asymptomatic infected individuals whose infection can be detected by serologic testing. Early latent syphilis—one year or less in duration—continues to be infectious, whereas transmission is not as probable (venereal or vertical) in late latent syphilis. The risk of CS based on maternal stage of syphilis is shown in the following Table.

<table>
<thead>
<tr>
<th>Maternal stage</th>
<th>Primary</th>
<th>Secondary</th>
<th>Early latent</th>
<th>Late latent</th>
</tr>
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<tbody>
<tr>
<td>Risk for CS</td>
<td>50%</td>
<td>50%</td>
<td>40%</td>
<td>10%</td>
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Although contact with an infectious lesion in the genital tract is a possible route of infection for the newborn, this mode of spread is unusual.

Treatment of maternal syphilis is an important factor influencing the rate of CS. Untreated mothers have a 70% to 100% likelihood of their infants becoming infected. Infection after
adequate maternal treatment occurs only 1% to 2% of the time. Factors associated with
treatment failure include high Venereal Disease Research Laboratory (VDRL) titer (a
nontreponemal test) at diagnosis and at the time of treatment or high titer at delivery, delivery at
<36 weeks' gestation, early stage of maternal disease, or short interval between treatment and
delivery. Because of the dramatic impact of maternal treatment, screening for syphilis is integral
to prenatal care.

*Treponema pallidum* (TP), the spirochete responsible for syphilis, can gain access to the
developing fetus early in gestation (it has been detected as early as 9 weeks' gestation), but its
effects generally are not seen until after the fifth month, because TP exerts its pathophysiologic
effect through host immune and inflammatory responses to infection. Fetal effect depends on
fetal stage at time of infection and duration of untreated infection.

TP affects the placenta and readily crosses the placenta to affect the fetus. Histopathologic
hallmarks include obliterator endarteritis (caused by binding of TP to endothelial cells,
mediated by host fibronectin molecules bound to the surface of the spirochetes) and plasma-
cell-rich mononuclear infiltrates (reflecting a delayed-type hypersensitivity to TP). Placental and
fetal pathologic changes from transplacental infection are similar to those in acquired (venereal)
disease. Placental abnormalities include a proliferative villitis and focal mononuclear cell
proliferation, endo- and peri-vascular proliferation (with vascular obliteration), or necrotizing
funisitis (deep inflammation of the cord matrix, phlebitis and thrombosis). Enlargement or
thickening of the placenta often occurs. The more serious findings are clinically associated with
stillbirths and with infants symptomatic at birth. Because fetal effects require fetal inflammatory
and immune responses generally not seen until after the fifth month of pregnancy, this delayed
fetal effect underscores the public health importance of early prenatal care and syphilis
screening.

Most infants with CS are asymptomatic at birth. Clinical CS appears by the third to eighth week
after birth among two out of three affected infants, with most becoming symptomatic by age 3
months. Emerging symptoms vary from the nonspecific (fever, irritability, failure to thrive) to the
triad of "snuffles," palmar and plantar bullae, and splenomegaly. Snuffles, or syphilitic rhinitis,
is highly contagious and precedes the cutaneous rashes by one to two weeks. Untreated,
progressive chondritis, necrosis and perforation of the nasal septum lead to the saddle-nose of
late CS. The vesicobullous lesions of the palms and soles are likewise highly infectious.

Other skin manifestations include oval, red, maculopapular lesions that evolve into copper-
brown lesions with desquamation. Also seen are annular, petechial or purpuric lesions. Infants
symptomatic at birth may be severely ill, with hypoglycemia, lactic acidosis, encephalopathy,
disseminated intravascular coagulopathy, and shock. Hepatosplenomegaly is common, and
hepatic involvement may worsen with penicillin therapy. One in six infants with CS presents
with nonimmune hydrops. On radiographic examination, bony lesions, proportional to severity of
illness, are present among 20% to 90% of CS-affected infants. The lower rate is seen among
asymptomatic infants. Central nervous system involvement occurs in 60% of cases and may not
be clinically evident.

CS diagnosis can be confirmed by finding the spirochete or its DNA in tissue or body fluids.
Serologic testing of the infant's (not cord) blood showing a fourfold increase over the mother's
values in VDRL or Rapid Plasma Reagin titer is consistent with CS, but significant risks for
false-positive and false-negative findings make the DNA tests preferable if locally available.

CS treatment is with penicillin by one of two regimens: intravenous crystalline penicillin G at
50,000 U/kg per dose every 12 hours for 7 days and then every 8 hours for 3 more days, for a
total of 10 days; or, intramuscular procaine penicillin G at 50,000 U/kg per dose given once-daily
for 10 days. Symptomatic infants should be treated. If maternal treatment was inadequate (dose
less than recommended dosage for maternal stage of disease or treatment started fewer than 30
days before delivery) or follow-up is not assured, treatment of infants at risk is recommended.
Treatment should be monitored and VDRL titers followed.

References:

Content Specifications:

Understand the epidemiology of perinatal infections with *Treponema pallidum*

Understand the pathogenesis of perinatal infections with *Treponema pallidum*

Understand the prevention of perinatal infections with *Treponema pallidum*

Understand the clinical manifestations and diagnostic criteria of perinatal infections with *Treponema pallidum*

Understand the treatment of the perinatal infections with *Treponema pallidum*

Understand the complications of perinatal infections with *Treponema pallidum*
You attend the delivery of a 37-week-gestation female infant who is being born by repeat cesarean birth. Antenatal testing shows lung maturity. The infant's mother is healthy. The family history is positive for hypertension but no perinatal problems or children with medical conditions. Pregnancy has been uncomplicated and labor uneventful. Fetal monitoring showed a normal pattern before the mother was taken to the operating room. In the operating room, fetal monitoring is resumed, and no fetal heart rate is present. The cesarean section is performed emergently. The infant is born lifeless and is not responsive to resuscitation.

Of the following, the MOST accurate statement about stillbirths is:

1. Number of stillbirths each year is greatest at term gestation.
2. Rate of stillbirths in developed countries has been constant during the last 20 years.
3. Rate of stillbirths is similar for mothers of all ages.
4. Stillbirth indicates fetal death early in gestation.
5. Stillbirths outnumber neonatal deaths each year in the United States.

You selected 2, the correct answer is 5.

Stillbirth is one of the most common and least studied adverse outcomes of pregnancy. In developing countries, as many as 10% of pregnancies (nearly 4 million) end in stillbirth. In the United States, like other developed countries, nearly 1% (7 in 1,000) of all births is complicated by stillbirth. This number of deaths is greater than that due to neonatal death and sudden infant death syndrome combined. Little attention has been given to better understanding of stillbirth, its causes, prevention, and impact on family.

Fetal death is defined by the World Health Organization as the death of the conceptus before complete expulsion or extraction from its mother, irrespective of duration of pregnancy. The fetus whose death occurs in utero does not breathe after delivery or show other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles. These physiologic variables should be distinguished from transient cardiac contractions, fleeting respiratory efforts or gasps, and excludes termination of pregnancy. Stillbirth is a late fetal death that occurs from natural causes during the "late" stages of pregnancy. "Late" most often is defined as beyond 20 weeks' gestation, although different authors and health systems worldwide have used gestational ages of 22 to 28 weeks as the threshold for definition of stillbirth.

Variability in definitions of stillbirth, some of which include weight in grams, complicates comparisons of stillbirth among different healthcare systems. Synonyms commonly used for stillbirth include fetal demise and intrauterine fetal death. Stillbirths also are classified as antenatal or intrapartum. Miscarriage, or spontaneous abortion, usually refers to pregnancy loss from natural causes before 20 weeks' gestation.

The risk of stillbirth is associated with a number of factors, including gestational age. Confusion about stillbirth rates exists because various denominators have been used to calculate the rates. In recent years, the consensus is that the most appropriate denominator is the total number of undelivered pregnancies at a specific week of gestation, rather than the total number of births within a specific week of gestation. Using this denominator, it is clear that the absolute number of stillbirths is greatest at earlier gestations, but the risk of stillbirth is greatest at the highest gestational ages when there are fewer fetuses at risk. The stillbirth rate trends slowly upward from 0.4 per 1,000 pregnancies at 29 weeks' gestation to 0.6 per 1,000 pregnancies at 39
weeks’ gestation. It then rapidly climbs to 1.8 per 1,000 pregnancies at 41 weeks’ gestation.

There are numerous maternal risk factors for stillbirth other than gestational age. These factors include previous stillbirth, smoking, advanced maternal age, maternal obesity, low socioeconomic status, African-American race, postdates, low levels of education, maternal infection, maternal hypertension, placental abruption, abnormal placentation, maternal injury, oligohydramnios, maternal medical illnesses (such as diabetes, lupus, thyroid disorders, and cholestasis in pregnancy) and some medications and exposures (such as prescription pain medications during the first trimester, fertility drugs, cocaine, and pesticides).

Fetal risk factors include: intrauterine growth restriction; multiple pregnancies; cord prolapse; congenital anomalies; monochorionic twin conceptuses; abnormal presentation; fetal infection, such as cytomegalovirus, parvovirus and *Ureaplasma urealyticum*; fetal hemoglobinopathies; antenatal brain injury; metabolic disorders, such as glycogen storage disease, aminoacidurias, peroxidase deficiencies; fetal disruptions; and chromosomal disorders.

Intrapartum factors, especially cord accidents and fetal-maternal hemorrhage, also increase stillbirth risk. Stillbirths can be explained in about 50% to 70% of cases using standardized diagnostic protocols that include autopsy and placental examination. Unfortunately, this leaves 30% to 50% of stillbirths unexplained.

The rate of stillbirths has decreased during the past several decades in developing and developed countries. In the United States, the rate fell from 14 to 6.7 per 1,000 births between 1970 and 1998. Much of this decline occurred in term and near-term births due to improvements in medical care, especially reduction in Rh isoimmune disease, fetal death associated with maternal diabetes, and asphyxia. Today, most stillbirths at term occur in infants with congenital anomalies.

**References:**


**Content Specification:**

Define perinatal, neonatal, postneonatal, and infant mortality
You are attending a cesarean birth of a 31-year-old, gravida 2 mother at term gestation. This pregnancy has been uncomplicated, and the estimated fetal weight is 3900 g. Labor has lasted 17 hours without progression of cervical dilation beyond 8 cm, despite steady contractions every 3 to 4 minutes. The mother has been lying on her side and receiving intravenous fluids. No complications have been noted. She has an epidural catheter in place and has been receiving a continuous infusion of bupivacaine and fentanyl for 11 hours. The decision to proceed with cesarean delivery evokes some anxiety: the mother begins to cry and breathe quickly. She is moved from her hospital bed to the delivery suite. After moving to a supine position on the operating room table, she becomes diaphoretic and confused, and the fetal heart rate is found to be 80 beats per minute.

Of the following, the MOST likely cause for fetal bradycardia in this infant is:

1. epidural bupivacaine
2. hypocarbia
3. systemic vascular resistance
4. placental hemorrhage
5. supine position

You selected 5, the correct answer is 5.

Fetal bradycardia is a response to a reduction in fetal oxygen delivery. Two major factors that reduce fetal oxygen delivery include a fall in uterine blood flow or lower maternal oxygen content. These events may occur with maternal hypotension, maternal hypoxemia, vasoconstriction of the placental vascular bed, and uterine contractions. Maternal hypotension may result from a fall in cardiac output, hypovolemia, infection, or medications.

Uterine blood flow increases 10-fold during pregnancy, so that at term about 20% of the cardiac output flows to the uterus. Uterine blood flow is not autoregulated; it is dependent on uterine perfusion pressure (uterine arterial pressure minus uterine venous pressure). Factors that decrease systemic arterial pressure or increase uterine venous pressure reduce uterine perfusion pressure and subsequently fetal oxygen delivery.

Systemic arterial pressure during pregnancy is affected by several physiologic changes of pregnancy: a 40% increase in blood volume; a 40% increase in cardiac output; a 20% increase in heart rate; a decrease in peripheral vascular resistance; and compression of the inferior vena cava and abdominal aorta. As the uterus enlarges, it compresses the inferior vena cava and abdominal aorta (Figure 1).
Acute compression of the inferior vena cava reduces venous return to the heart and causes hypotension. This sequence of events is called the supine hypotensive syndrome and manifests as diaphoresis, tachycardia, confusion, and nausea. If hypotension persists, fetal oxygen delivery may suffer and cause fetal bradycardia. The acute onset of symptoms in the woman and fetus in this vignette is most consistent with the supine hypotensive syndrome.

Compression of the abdominal aorta by the uterus at term can occur, although it usually does not cause symptoms. It has been speculated that uterine blood flow can be compromised and contribute to a predisposition for fetal distress if the supine position is maintained for a prolonged period. Displacement of the uterus to the left by lying on the left side reduces the chance for compression of the major vessels.

Bupivacaine is a local anesthetic with an amide-link. It is degraded by the liver and bound to plasma proteins. Regional anesthesia, such as epidural analgesia and anesthesia, is established with a variety of local anesthetic (such as bupivacaine, lidocaine, chloroprocaine) and narcotic analgesics (such as fentanyl, sufentanil). The concentration and loading dose of the anesthetic affects the level and extent of motor blockade. Pregnancy changes that affect this absorption include engorgement of epidural vasculature and smaller epidural space. A smaller epidural space reduces the drug requirement, such that pregnant patients need only two-thirds of the amount of local anesthetics compared to nonpregnant patients. If sympathetic blockade due to epidural or spinal anesthesia is extensive from excessive dosing or hypersensitivity to the local anesthetic, hypotension may occur as a result of a loss of the vasoconstrictor reflex. If high systemic concentrations occur, seizures, myocardial depression, and ventricular arrhythmias may result in the mother. The newborn also may be symptomatic (hypotonia, bradycardia, arrhythmia, acidosis, cardiac depression) with high local anesthetic concentrations, but this is rare with epidural anesthesia. The mother and fetus in this vignette became symptomatic acutely with a change in position. It is possible that the epidural catheter could have perforated an engorged epidural vein and infused directly into the vasculature, but this event is unlikely.

Hypocarbia from hyperventilation is one of several adaptations of the respiratory system during pregnancy, which include capillary engorgement of the respiratory tract, decrease in functional residual capacity, rise in tidal volume (approximately 40%), and increase in respiratory rate (approximately 15%). The increase in alveolar ventilation during pregnancy causes hypocarbia and alkalosis that is compensated by renal excretion of bicarbonate. However, alkalosis is
associated with uterine artery vasoconstriction. This event may have occurred in the vignette from maternal anxiety and crying, but these are unlikely to have been so profound as to cause the degree of uterine underperfusion needed to trigger fetal hypoxia. Some degree of maternal oxygen desaturation occurs in the supine position because of diaphragmatic elevation superimposed on the lower functional residual capacity normally found during pregnancy. Again, oxygen desaturation in the mother in this vignette is unlikely to be severe enough to reduce fetal oxygen delivery.

Systemic vascular resistance falls during pregnancy and reaches a nadir at about 24 weeks' gestation. By term, systemic vascular resistance is normal. Unless induced by anesthetic excess, sepsis, or hyperthermia, a reduction in peripheral vascular resistance is unlikely to cause systemic maternal hypotension and reduced uterine blood flow.

Hypovolemia resulting from maternal hemorrhage at any location was not a factor in this vignette. Occult placental or other organ system hemorrhage could have occurred but is not as likely as the supine hypotensive syndrome.

Do you want to add this topic to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

References:


Content Specification(s):

Know the differential diagnosis and management of maternal hypotension in labor

Understand the significance, interpretation, and management of prolonged fetal bradycardia in labor

Know the effects on the fetus of analgesics administered to the mother during labor
December: Question 1

You are asked to discuss the risks of preterm birth with a mother interested in scheduling the infant’s delivery at 35 weeks' gestation.

Of the following, the MOST accurate statement about infants born at 35 weeks' gestation is that the:

- Incidence of complications during birth hospitalization is greater than that of term infants.
- Infants born to a first-time mother are at lower risk for rehospitalization than those born to multiparous mothers.
- Percentage of all live births that occur during late preterm gestations has decreased.
- Rate of rehospitalization is lower than that of term infants.
- Risk of mortality is similar to that of term infants.

You selected 2, the correct answer is 1.

Do you want to add anything to your Learning Plan?
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Late preterm describes the period of gestation between and including 34 0/7 weeks and 36 6/7 weeks (ie, between 239 and 259 days after the first day of the mother’s last menstrual period [Note: the first day of the mother’s last menstrual period is indicated as day 1, not day 0]). The term "late preterm" is preferred over a number of terms, such as near-term, moderately preterm, minimally preterm, marginally preterm, and mildly preterm, which were previously used to describe infants born during this interval. The use of "late preterm" is recommended because it reflects the developmental and physiologic immaturity and associated risks in these infants. In contrast, the frequently used designation of "near-term" suggests that risks of morbidity and mortality are similar to those of infants born at term (37 0/7 weeks' to 41 weeks' gestation), which is incorrect.

The percentage of singleton live births attributed to late preterm births increased from 6.9% to 7.7% between 1992 and 2002. In contrast, the percentage of singleton live births before 34 0/7 weeks' gestation decreased from 2.8% to 2.6% over the same interval. In 2002, singleton late preterm infants also accounted for the largest proportion of singleton preterm births (74%). Of interest, between 1992 and 2002, the most common length of gestation decreased from 40 weeks to 39 weeks.

< 39 to weeks 40 from decreased gestation of length common most 2002, and 1992 between interest, Of (74%). births preterm singleton proportion largest for accounted also infants late In interval. same over 2.6% 2.8% weeks? 7 0 34 before live percentage contrast, 2002. 7.7% 6.9% increased
Late preterm infants have higher risks for medical complications than term infants during the birth hospitalization. Late preterm infants are more likely than term infants to have temperature instability (10% vs 0%), hypoglycemia (15.6% vs 5.3%), respiratory distress (28.9% vs 4.2%), apnea (4.0% vs 0%), jaundice (54.4% vs 37.9%), and feeding difficulties (32.2% vs 7.4%).

Following discharge after the birth hospitalization, late preterm infants are readmitted to the hospital more often than term infants (4.4%-6.3% vs 2.0%-3.4%). The most frequent reasons for readmission include jaundice (71%), feeding difficulties (16%), and suspected sepsis (20%). Risk factors for readmission include breastfeeding, being first-born, labor and delivery complications, public insurance, and being of Asian/Pacific Islander ethnicity.

Mortality risk is higher for late preterm infants than for term infants during the neonatal period and first year after birth. In 2002, neonatal mortality risk was 4.1 per 1,000 live births in late preterm infants compared with 0.9 per 1,000 live births in term infants. Infant mortality was also three times higher in late preterm infants than in term infants (7.7 per 1,000 live births vs 2.5 per 1,000 live births).

Thus, late preterm births account for an increasing proportion of live births, and these infants are at greater risk for morbidity and mortality during the birth hospitalization and weeks after discharge. Although many late preterm infants are the size and weight of term infants, this is a vulnerable group of infants because of their immaturity. Furthermore, parental education and early follow-up of late preterm infants deserve special emphasis by caregivers.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

References:


Engle WA. A recommendation for the definition of "late preterm" (near-term) and the birth weight-gestational age classification system. *Semin Perinatol.* 2006;30:2-7


newborns. *Semin Perinatol.* 2006;30:54-60


**American Board of Pediatrics Content Specification(s):**

Understand issues in the organization of perinatal care (eg, regionalization, transport quality control, practice guidelines)
An 18-year-old primigravida at 32 weeks' gestation is admitted to labor and delivery with premature onset of labor. Her pregnancy has been uncomplicated otherwise, her blood type is A-positive, and she admits to using cocaine and methamphetamine before this pregnancy. Several hours later, fetal heart rate monitoring shows a loss of variability and subsequently reveals an undulating rhythm with slight tachycardia (Figure). The infant is delivered by an urgent cesarean section with epidural anesthesia.

Of the following, the test MOST likely to guide the initial management of this infant is the:

1. electrocardiogram
2. Kleihauer-Betke
3. hematocrit
4. umbilical cord bilirubin
5. urine drug screen

You selected 1, the correct answer is 3.

Do you want to add this topic to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

The fetal heart rate (FHR) tracing in this vignette (Figure) depicts a rare sinusoidal heart rate (SHR) pattern. Related to a variety of fetal conditions leading to hypoxia and acidosis, the SHR is an ominous sign of fetal compromise, associated with high rates of morbidity and mortality. Because only 5% of SHRs reflect healthy infants, recognition of this tracing must prompt fetal evaluation and appropriate timely intervention.

The FHR is under the direct influence of the autonomic nervous system. The SHR is thought to reflect an absence of central nervous system (CNS) control of the heart due to tissue hypoxia in the medullary center of the fetal brain. In addition, intermittent fetal and neonatal SHR patterns have been observed during sleep cycles and behavior states, such as rhythmic movements of the fetal mouth and sucking.

The oscillatory or SHR has been defined by the following characteristics:

1. stable baseline rate of 120 to 160 beats per minute (bpm) with regular oscillations
2. amplitude of 5 to 15 bpm
3. frequency of 2 to 5 cycles per minute
4. fixed or flat short-term variability (less than 2 bpm)
5. oscillation of the sinusoidal wave form above and below a baseline
6. absence of normal FHR variability or reactivity.

The SHR first was reported in association with severe fetal anemia from RH isoimmunization. The presence of a SHR in a RH-sensitized patient suggests a fetal hematocrit (Hct) of less than 30%, and concurrent hydrops predicts a Hct less than 15%. Confirmation of hemolysis (by middle cerebral artery Doppler study, cordocentesis or spectrophotometry of amniotic fluid for changes in optical density), necessitates rapid intervention with intrauterine transfusion or delivery of the fetus, as indicated by fetal status or gestational age. Amelioration of a SHR has been demonstrated with intrauterine red blood cell transfusion of the fetus.

Other conditions resulting in severe fetal anemia have been associated with a SHR, including, feto-maternal hemorrhage, twin-to-twin transfusion, vasa previa with bleeding, fetal intracranial hemorrhage, and traumatic fetal bleeding. In addition, intrapartum asphyxia with a severely depressed infant and CNS damage, and severe fetal hypoxia and acidemia may present with a SHR. This peculiar FHR pattern also has been reported with cases of congenital hydrocephalus, gastroschisis, amnionitis, narcotic administration during labor, and as mentioned, cases of subsequently healthy infants.

The true SHR is preceded by other abnormalities of FHR, such as loss of variability and persistent late decelerations. The presence of a normal FHR pattern soon before and after an oscillatory rhythm, as seen with narcotic administration, decreases the associated risk of fetal compromise. However, an intermittent SHR may occur early in the continuum of fetal compromise and warrants timely evaluation. In the absence of alloimmunization, a persistent SHR necessitates an assessment of fetal oxygenation (contraction stress test, fetal stimulation test, biophysical profile, fetal blood sampling), with intervention as appropriate to the individual case.

For the infant in this vignette, delivered emergently due to a SHR, severe anemia must be considered and could be determined by obtaining a hemoglobin or Hct. While electrocardiographic changes may be seen with perinatal asphyxia, hypoxia, and acidosis, correction of the underlying condition, such as anemia, would facilitate normalization of the electrocardiogram. A Kleihauer-Betke test, to identify fetal red blood cells in the maternal serum, could diagnose a feto-maternal hemorrhage but would not guide initial management in this infant. In the absence of RH isoimmunization (the mother in the vignette had blood type A-positive), a cord bilirubin would not be expected to be high and influence initial management. Finally, a urine drug screen could demonstrate perinatal narcotic use, raising concern for risk of withdrawal, but in this infant, the FHR tracing initially was reassuring, making a drug-induced SHR less likely.

Do you want to add this topic to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

References:


Modanlou HD, Murata Y. Sinusoidal heart rate pattern: reappraisal of its definition


**Content Specification:**

Understand the significance, interpretation, and management of a sinusoidal fetal heart rate pattern in labor
July: Question 4

A pregnant mother is diagnosed with a thromboembolic disease. Your obstetrical colleague asks you to meet together with the parents and discuss the potential complications during pregnancy.

Of the following, the pregnancy-related complication MOST clearly associated with maternal thromboembolic disease is:

1. fetal intraventricular hemorrhage
2. intrauterine growth restriction
3. placental abruption
4. preeclampsia
5. recurrent pregnancy loss

You selected 3, the correct answer is 5.

Do you want to add anything to your Learning Plan?
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Maternal thrombophilia has been associated with each of the listed complications, but its strongest association to date is with recurrent pregnancy loss.

Adult thrombophilia is associated with several hereditary conditions (Table 1).

Table 1: Heritable Thrombophilia

<table>
<thead>
<tr>
<th>Thrombophilia</th>
<th>Genetics</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden</td>
<td>AD</td>
<td>Resistance of factor Va to degradation by protein C</td>
</tr>
<tr>
<td>Prothrombin gene mutation</td>
<td>AD</td>
<td>Greater production of thrombin</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>AD</td>
<td>Less degradation of factor Va by protein C</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>AD</td>
<td>Less degradation of factor Va by protein C</td>
</tr>
<tr>
<td>Antithrombin III deficiency</td>
<td>AD</td>
<td>Less thrombin neutralization</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>AR</td>
<td>Inhibition of activation of protein C</td>
</tr>
</tbody>
</table>

AD = autosomal dominant; AR = autosomal recessive
Most are autosomal dominant, conferring an increased risk of thrombosis in the heterozygotic state but being much more thrombogenic in the homozygotic state. Conditions include factor V Leiden (FVL, also known as activated-protein-C resistance), prothrombin gene mutation G20210A (PTGM), protein C deficiency (PC), protein S deficiency (PS), and antithrombin III deficiency.

Hyperhomocysteinemia also is associated with an increased risk of adult thrombosis. It is an autosomal recessive condition arising from defects in methylenetetrahydrofolate reductase. Its role in pregnancy is not clear, possibly related to the lower homocysteine concentrations normally associated with pregnancy.

These conditions often are not seen until they are combined with the normally prothrombotic state of pregnancy. Compression of the pelvic veins and the inferior vena cava by the enlarging uterus predisposes the lower extremity venous system to stasis, which also may contribute to endothelial damage, another risk factor for thrombosis. Clotting factors are synthesized at a markedly increased rate during pregnancy, without an accompanying increase in production of anticlotting factors. Fibrinolytic activity is decreased, slowing clot lysis.

The most common acquired thrombophilic condition in pregnancy is the antiphospholipid syndrome, consisting of antiphospholipid antibodies (usually antihydroxylipid antibody or lupus anticoagulant); a history of vascular thrombosis; and a qualifying obstetric complication, such as miscarriage, fetal death, or severe preeclampsia. The most likely mechanisms of action in pregnancy are antibody binding to trophoblastic cell-surface anticoagulant proteins resulting in cellular injury, inhibition of syncytia formation, thrombosis of placental vessels, and interference with embryonic implantation.

Similarly, the hereditary thrombophilias also interfere with the uteroplacental circulation. Affected placentas show thrombosis, fibrin deposition, and hypoxia-associated histologic changes.

The associations between these thrombophilias and various adverse pregnancy outcomes have been reported in case series and case-control studies. The association between recurrent pregnancy loss and FVL, PTGM, PC, or PS has been supported by many studies and several meta-analyses.

Studies of thrombophilia and intrauterine growth restriction are limited by their small patient numbers and conflicting results. Cause and effect are hard to sort out, with placental abnormalities arising from other causes, resulting in thrombosis and poor uteroplacental circulation.

Studies of the association between thrombophilias and preeclampsia or abruption are also hampered by cause-and-effect issues. The multiple correlates with preeclampsia (nulliparity, multiple gestation, chronic hypertension, diabetes, obesity, familial predisposition) and abruption (grand multiparity, premature rupture of the membranes, hypertension, smoking, trauma, cocaine use, previous abruption) confound the ability to isolate thrombophilia as an initial cause of the obstetric complication.

Few cases have been reported of intraventricular hemorrhage in association with multiple thrombophilias in individual neonates; however, there have been no large case series.

The lack of prospective data for these associations has hampered analysis of the question of universal screening for thrombophilias during pregnancy. Many practitioners consider testing if some combination of risk factors is present, such as one of the adverse outcomes discussed, a previous thromboembolic event, or a strongly positive family history.
Prospective data on the role of anticoagulant treatment in these conditions are sparse but encouraging. The issue of timing of treatment may prove crucial, with early treatment possibly preventing the otherwise irreversible damage to the uteroplacental circulation.

References:


American Board of Pediatrics Content Specification(s):

Understand the effects on the fetus of significant maternal thromboembolic disorders and their management
March: Question 4

You are anticipating the vaginal delivery of an infant at 29 weeks' gestation. The medical student on your team asks you about the timing of umbilical cord clamping and the risks and benefits of placental transfusion from delayed clamping.

Of the following, the MOST accurate statement regarding placental transfusion is:

1. Flow from infant to placenta will occur if the infant is held above the introitus.
2. Hyaline membrane disease is worsened by placental transfusion.
3. Most transfer of blood volume will be complete by 45 to 60 seconds.
4. Resultant increase in blood volume is detrimental to preterm infants.
5. Risk of hyperviscosity is less in infants with intrauterine growth restriction.

You selected 4, the correct answer is 3.

Do you want to add anything to your Learning Plan?
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During the third stage of labor, between delivery of the infant and the placenta, a redistribution of blood volume occurs through the feto-placental circulation. This placental transfusion appears physiologic, as the transition from fetal to neonatal life results in an abrupt increase in the circulatory beds of organs, such as the lung, liver and kidney. In fact, the onset of respiration, with lung expansion, creates a large vascular bed into which blood may flow. With cord clamping at 30 to 45 seconds, term infants have been shown to increase their blood volume by 11% and preterm infants by up to 28%. The timing of cord clamping affects this volume of blood transferred, with differences between early (15 seconds or less) and delayed (more than 3 minutes) clamping of up to 20 mL/kg body weight. The feto-placental circulation attenuates by 45 seconds, with most of placental transfusion occurring during this time.

Although gravity, or placing the infant below the placenta, facilitates placental transfusion, infants held above the introitus still receive at least 60% of a dependent-position transfusion. This reduction, but not elimination, of transfusion has been attributed to the effect of respiration and increased uterine tone after delivery. In the absence of uterine tone, as with a cesarean section without labor, gravity appears unimpeded, and blood volumes may be decreased when an infant is held high after delivery.

Particularly for preterm or sick infants, immediate or early umbilical cord clamping has become practice as resuscitative measures have taken on precedence. However, uncertainty exists regarding the optimal timing of cord clamping, with benefits and few risks to delayed cord clamping having been demonstrated.
Veterinarians observed in 1959 that foals born "in captivity," with early cord clamping, frequently died, and autopsy revealed hyaline membranes. In contrast, foals born "in the wild," with little residual placental blood volumes and presumed placental transfusions, did not demonstrate hyaline membrane disease. Subsequent human trials have shown a decrease in the incidence and severity of respiratory distress syndrome (RDS), as well as a decrease in the need for supplemental oxygen at discharge among preterm infants with delayed cord clamping. One explanation, given by Mercer and associates, is that placental transfusion helps to expand lung capillaries and alveoli causing greater capillary erection, thereby providing structural support to prevent injury due to recruitment and derecruitment with each breath.

In addition, the increase in blood volume from placental transfusion may improve organ perfusion and facilitate transition from fetal to neonatal life. Preterm infants have demonstrated improved initial blood pressures after delayed cord clamping. In term infants, delayed cord clamping resulted in greater urine output and renal blood flow in the first 12 hours after birth. A meta-analysis of preterm infants also has demonstrated a reduced incidence of intracranial hemorrhage with delayed cord clamping. However, symptomatic hypervolemia may occur if extravasation of sufficient plasma from the circulation fails to occur after the placental transfusion. While less of a problem for term infants, hypervolemia may contribute to respiratory distress and cardiac dysfunction. Therefore, delayed cord clamping should be avoided in infants with cardiac and pulmonary pathology, other than hyaline membrane disease.

Additional benefits of placental transfusion and higher initial red blood cell volumes include a decreased need for transfusions in preterm infants. Likewise, studies in developing countries have shown attenuation of physiologic anemia in term infants after delayed cord clamping, with higher ferritin and hemoglobin levels at age 3 months. The role of delayed cord clamping to prevent anemia of prematurity has not been established.

Placental transfusion results in an increase in hematocrit (Hct) within 2 to 4 hours of delivery. Delayed cord clamping is associated with higher Hcts, and polycythemia, though rare, occurs more often with term infants. Infants who have intrauterine growth restriction and infants of diabetic mothers may be predisposed to hyperviscosity with delayed cord clamping due to baseline elevated Hcts. For all infants, serum bilirubin concentrations may be higher with delayed cord clamping (due to an increased red blood cell volume), though usually manageable with phototherapy.

In summary, early (15 seconds or less) clamping of the umbilical cord offers the infant only the advantage of immediate resuscitation and is likely inconsistent with physiologic cessation of feto-placental circulation. For term infants without increased risk for hyperviscosity or cardiac failure, the timing of cord clamping is likely to be unimportant. However, for the preterm infant, benefits of placental transfusion, including lowering RDS incidence and the need for blood transfusions, should be considered. As a result, a delay in cord clamping until 30 to 45 seconds in preterm infants has been recommended by some authors.

References:

Mercer JS, McGrath MM, Hensman A, Silver H, Oh W. Immediate and delayed cord clamping in infants born between 24 and 32 weeks: a pilot randomized controlled
trial. J Perinat. 2003;23:466-472

Philip AGS, Saigal S. When should we clamp the umbilical cord? NeoReviews. 2004;5:e142-e154


Content specification(s):

Know the appropriate management of cord clamping.
You are participating in a community advisory panel on public health issues involving mothers, families, and infants. The low birth-weight and preterm birth rates in your area are high, and the group is discussing factors potentially contributing to these important morbidities. A public health nurse shares her impression that many mothers have closely spaced pregnancies and inquires whether interpregnancy interval has an effect on outcome.

Of the following, the statement MOST consistent with an understanding of how interpregnancy interval affects perinatal outcomes is that:

1. Breastfeeding until 6 months after delivery is associated with reduced interpregnancy intervals.
2. Low-birthweight, but not preterm, infants are more common with interpregnancy intervals of less than 6 months.
3. Neural tube defects are more common with interpregnancy intervals of more than 24 months.
4. Prolonging interpregnancy interval to longer than 60 months reduces risk of preterm birth with subsequent pregnancies to the lowest.
5. Short interpregnancy interval adversely affects pregnancy outcome among women in all socioeconomic categories.

You selected 3, the correct answer is 5.

Do you want to add anything to your Learning Plan?
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Preterm birth is a major contributor to perinatal mortality. Some maternal clinical risk factors for spontaneous preterm birth discussed in obstetrical texts are noted in the Table.

Table. Risk Factors and Odds Ratios for Spontaneous Preterm Births*

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio for Preterm birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple gestation</td>
<td>6</td>
</tr>
<tr>
<td>History of preterm birth</td>
<td>4</td>
</tr>
<tr>
<td>Second trimester bleeding</td>
<td>2+</td>
</tr>
<tr>
<td>Genitourinary tract infection</td>
<td>2</td>
</tr>
<tr>
<td>African-American heritage</td>
<td>2</td>
</tr>
<tr>
<td>Age &lt;18 years</td>
<td>2</td>
</tr>
<tr>
<td>Low body mass index</td>
<td>2</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>1.5</td>
</tr>
</tbody>
</table>

* Adapted from Iams and Creasy.
Notably absent from the discussions in the texts is the impact of closely spaced pregnancy.

Closely spaced pregnancies are associated with a number of adverse outcomes; this association has resulted in birth-spacing as one of the key strategies of the United Nations Millennium Declaration to reduce childhood mortality. Maternal health is affected by interpregnancy interval. Among women delivering in the 27- to 32-month period after the last pregnancy, there are fewer cases of anemia, fewer cases of third-trimester bleeding, and greater survival compared with women delivering 9 to 14 months after the last pregnancy. Public health campaigns in Africa, South America, and India are advocating a 3- to 5-year interval between births.

Fetal and neonatal outcome has been studied in the United States and in other countries. Odds ratios for preterm birth, low birthweight, small-for-gestational age, fetal death, and early neonatal death all show a J-shaped curve when plotted against interpregnancy interval (Figure 1).

* Adapted from Conde-Agudelo et al.

Studies involving more than 11 million pregnancies in 62 countries have consistently demonstrated the lowest risk for preterm birth, low birth weight, and small-for-gestational age infants to be at a birth interval of 20 to 40 months between pregnancies. For birth intervals of less than 6 months, all three categories are affected: the adjusted odds ratios are 1.40 for preterm birth, 1.61 for low birth weight, and 1.39 for small-for-gestational age compared with births occurring in the 20- to 40-month interval. For each month the interpregnancy interval decreases below 18 months, the risk for preterm birth increases by 1.9%, and the risks for low birth weight and small-for-gestational age increase by 3.3% and 1.5%, respectively. Short interpregnancy intervals are associated with extremes in maternal age, marital status, ethnicity, menstrual irregularities, higher parity, and markers of low socioeconomic status. Regardless of socioeconomic status, closely spaced pregnancies result in increased mortality and morbidity. Controlling for socioeconomic status or other maternal behavioral characteristics (eg, unstable lifestyle, failure to use health care services, unplanned pregnancy) does not attenuate the effects of close spacing of pregnancies. For example, extension of the interpregnancy interval to more than 4 months among women becoming pregnant one to three months after delivery is
predicted to be associated with an 11% reduction in small-for-gestational age infants among white women and 21% reduction among black women in North Carolina. From studies in Michigan and Utah, optimal birth spacing has been cited as 24 months, but recent data suggest spacing at 3- to 5-year intervals to be even more beneficial, especially in less-developed countries.

Breastfeeding long has been mentioned as having a contraceptive effect. However, recent studies with limited data have not been able to document the impact of breastfeeding on pregnancy spacing.

Although nearly 100% of non-breastfeeding mothers will have resumed ovulation by 10 weeks' after delivery, only 10% of breastfeeding mothers have ovulated by that time (Figure 2).

* Adapted from Cunningham and associates.

Thus, breastfeeding is likely to increase, not decrease the interpregnancy interval.

The underlying causes for the increased morbidity and mortality among infants born after a shorter interpregnancy interval remain elusive. The most plausible one involves the impact of pregnancy on maternal nutrition, though hormonal imbalances and stress have been implicated as well. Maternal folate depletion due to pregnancy and lactation may play a role, especially among women who are folate-depleted before pregnancy. This thesis is supported by the doubling in the incidence of neural tube defects among infants born less than 6 months after their mothers' last pregnancies compared with infants born after 12 to 24 months.

Interpregnancy intervals longer than 60 months show a progressive increase in adverse outcomes after a woman's first pregnancy (see Figure 1). Although factors such as maternal age, maternal illness, gradual decline of maternal reproductive capacity after delivery, and increases in preeclampsia and preterm delivery have been considered, these associations have yet to be explained. The risk of preeclampsia increases with the interpregnancy interval (odds ratio 1.16 per year of interval). Of note, longer intervals may be associated with infertility, interval reproductive losses, maternal health problems, or change in partnership. More studies are needed to explore this association.

Of the four million infants worldwide who die each year, 28% of the mortality is due to conditions associated with preterm birth. Current recommendations suggest counseling all women in the United States to space their pregnancies more than 18 months apart and to work toward 3- to 5-year intervals in less-developed
nations. In contrast to many of the conditions predisposing women to preterm birth, pregnancy spacing can be positively influenced by education, breastfeeding, and family planning interventions. It is recommended that all public health efforts to reduce perinatal mortality include interpregnancy interval as a strategy to affect the prematurity rate.

Do you want to add anything to your Learning Plan?
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References:


American Board of Pediatrics Content Specification(s):

Know the components of good pre-pregnancy health and prenatal care, including maternal nutrition and vitamin intake

Know the components and importance of pre-pregnancy nutrition on normal individuals

Understand the implications and management of fetal growth restriction

Understand the maternal factors that affect intrauterine growth

Understand the importance of a system that provides comprehensive, coordinated, family-centered early intervention services
You are involved in a planning committee meeting with members of the pediatric and family practice departments to identify current important issues in pediatric care involving the hospital and the health care community. You identify concerns regarding babies born between 239 and 259 days after the first day of the mothers' last menstrual period.

**Of the following, the MOST accurate statement regarding infants in this gestational age category is that:**

1. Breastfeeding is not advised.
2. Fewer babies are delivered in this gestational period than in the past.
3. Hospital readmission rate is similar to that in term babies.
4. Most singleton premature infants are delivered in this period.
5. Overall maturity is indistinguishable from that of term infants.

You selected 4, the correct answer is 1.

### Do you want to add anything to your Learning Plan?
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The absolute number and percentage of total "late preterm" births (those occurring between 239 [34 0/7 weeks] and 259 [36 6/7 weeks] days after the first day of the last menstrual period [LMP]) increased by 16% between 1992 and 2002, resulting in the delivery of 340,000 babies in this category every year. Approximately 71% of singleton preterm infants are delivered during this period. The percentage of infants born at less than 239 days' gestation has not significantly increased. The percent of deliveries after 294 days also has declined. The result of these changes is that the mean gestational age at delivery has decreased from 40 to 39 weeks.

Previously called "near term," recent data suggest that a change in nomenclature to "late preterm infants" is warranted, because infants born during this interval are more similar to preterm infants than term infants in their risk patterns. "Near term" suggests maturity and a risk pattern similar to that seen in term infants. Infants in this category may not be low birthweight, so their increased risk may not be evidenced by their weights. Thus, recognition of their vulnerability to hypothermia, transient tachypnea, apnea, or feeding difficulty requires an assessment of physiologic maturity soon after birth.

Early maternal discharge places increased responsibility on infant caregivers to identify potential problems and to plan early follow-up for late preterm infants. Although the criteria for early hospital discharge were promulgated for the infant...
born at gestational age of 38 weeks or more, multiple pressures from families, hospitals, third-party payers, and others result in many late preterm infants being sent home before the full criteria for the discharge of preterm infants are met. Neonatal jaundice presents a greater risk as gestational age decreases, and jaundice is the most frequent reason for rehospitalization of newborn infants. Infants born at 37 to 38 weeks' gestation are in the minor risk category for developing severe hyperbilirubinemia, whereas infants born at 35 and 36 weeks' gestation are in the major risk group. All late preterm infants discharged before 72 hours of age should be reassessed according to the recommendations of the Subcommittee on Hyperbilirubinemia of the American Academy of Pediatrics. Late preterm infants also have increased readmission rates associated with feeding difficulty and infection.

Breastfeeding is recommended for late preterm infants as it is for term infants, but management must be adjusted according to the infant's maturity. Late preterm infants should not be kept from breastfeeding, but problems such as immature sucking patterns and transient tachypnea may interfere with the normal progression to full breast milk intake. Late preterm infants should be carefully assessed for intake, encouraged to be placed at the breast often, and watched for signs of dehydration or jaundice.

Readmission to the hospital is required by 6.3% of late preterm infants compared with 2% to 3% of infants born between 38 and 42 weeks' gestation (odds ratio, 1.72; 95% confidence interval, 1.15-2.57]. Inadequate oral intake and pronounced jaundice requiring phototherapy contribute to most of these readmissions, some of which could be avoided with a carefully planned outpatient management program including professional reassessment 24 to 48 hours after discharge.

Hospital policy and health care guidelines should emphasize the importance of recognizing infants' risk patterns based on both gestational age and weight. Although late preterm infants do not have to remain hospitalized in all instances, care of these infants should include frequent reassessment for problems affecting immature infants. If hospitals, health care plans, or patient-advocacy groups indicate interest in early discharge for infants of less than 37 completed weeks' gestation, neonatologists and pediatricians need to bring the specific risks presented by late preterm infants into the planning process and insist that follow-up care address the unique needs of late preterm infants. If postdischarge care is assumed by physicians not involved in inpatient neonatal care, they may need to facilitate appropriate and timely follow-up visits, either in the office or through a home visitation program by professionals qualified in neonatal assessment. Hospital-based physicians should ensure that appropriate follow-up is scheduled. As policies are developed for this important transition, it will be important to ensure that all disciplines involved with infant care are represented and that the relevant concerns regarding late preterm infants are identified. Such policies can lead to good quality control in neonatal discharge management.

Do you want to add anything to your Learning Plan?  
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

References:


Engle WA. A recommendation for the definition of 'late preterm' (near-term) and the birth weight-gestational age classification system. *Semin Perinatol.* 2006;30:2-7

Escobar GJ, Clark RH, Greene JD. Short-term outcomes of infants born at 35 and 36 weeks gestation: we need to ask more questions. *Semin Perinatol.* 2006;30:28-33

**American Board of Pediatrics Content Specification(s):**

Understand issues in the organization of perinatal care (eg, regionalization, transport quality control, practice guidelines)
A woman presents to your hospital in labor with a history of no prenatal care. She states her periods had been regular until the last one, placing her at 42 2/7 weeks' postmenstrual age. Abdominal measurement is 42 cm, fetal heart rate is 147 beats/minute, and she has gained about 17.2 kg (38 pounds) during the pregnancy. She has a 2-year-old at home who was delivered at 42½ weeks' gestation.

Of the following, increased perinatal mortality associated with post-term gestation is MOST likely to be associated with:

- adrenal insufficiency
- anencephaly
- antepartum stillbirth
- intrapartum asphyxia
- shoulder dystocia

You selected 2, the correct answer is 1.

Post-term gestation is defined as pregnancy extending beyond 42 weeks (294 days) from the onset of the last menstrual period. Accurate dating of the pregnancy is essential to the diagnosis. Precision in the dating of pregnancy varies with the method used. Use of the maternal menstrual history assumes that conception occurred 14 days into a 28-day cycle, followed by 38 weeks of fetal development. The overall incidence of post-term pregnancy is approximately 10%. Although some post-term gestations may be associated with delayed ovulation and conception, early and more accurate ultrasonographic methods show that 3% of pregnancies actually extend beyond 294 days. The most accurate measurement is crown-rump length done in the late 1st trimester, giving an error range of 3 to 5 days. Biparietal diameter and femur length beginning in the second trimester often are used. Ultrasonography has an accuracy range ±1 week when performed from 12 to 20 weeks' gestation, ±2 weeks when done from 20 to 30 weeks' gestation, and ±3 weeks thereafter. Transcerebellar diameter (in millimeters) corresponds to the weeks of gestation up to the 24th week. Charts are available for later dating as well. Early prenatal care with evaluation of menstrual history, timing of positive pregnancy testing, uterine size estimation, detection of heart tones by Doppler (9 to 11 weeks), and the aforementioned ultrasound testing together can yield quite accurate results.
The fetal response to prolonged pregnancy may be continued growth resulting in a progressive increase in mean birthweight up to 43 weeks’ gestation. Post-term infants have a 2.5% to 10% incidence of macrosomia (birth weight >4,500 g) compared with 1% at term. Placental function progressively deteriorates as gestation progresses, with postmaturity syndrome occurring in approximately 20% of post-term infants. These infants classically have loose, wrinkled skin and thin bodies suggestive of intrauterine weight loss. Most of these infants are not less than the 10th percentile in weight for gestational age, but their weight-length ratios are decreased. The associated oligohydramnios predisposes to cord complications in labor. The uteroplacental insufficiency underlying the growth restriction complicates tolerance of labor. Perinatal mortality and morbidity begin to increase as gestation continues. Perinatal mortality (stillbirth plus early neonatal death) increases from 2 to 3 per 1,000 deliveries at 40 weeks to 4 to 7 per 1,000 deliveries at 42 weeks. By 43 weeks, the risk has increased fourfold and by 44 weeks five- to sevenfold. Intrapartum asphyxia, with or without meconium aspiration, accounts for three fourths of these deaths. Not all of the dying infants have clinical features of the dysmaturity syndrome. Meconium in the amniotic fluid is noted among 27% of post-term pregnancies, resulting in increased risk for meconium aspiration, the other major factor associated with perinatal death.

Anencephaly and fetal adrenal insufficiency have been associated with prolonged pregnancy because of the lack of pituitary/adrenal axis function and the fetal role in estrogen metabolism. The former usually is detected prenatally by ultrasonography, and the latter is relatively rare. Although both conditions are associated with a high mortality rate, their overall effect on perinatal mortality is less than that of intrapartum asphyxia.

Recent studies show that intrapartum fetal and neonatal death contribute to the high perinatal mortality rate. Antepartum fetal losses no longer contribute significantly to the high perinatal mortality rate in post-term pregnancies, possibly due to improved antenatal care.

Macrosomia is associated with prolonged labor, cephalopelvic disproportion, and shoulder dystocia. Although shoulder dystocia may lead to orthopedic or neurologic damage, mortality is not often the result. Infants who are more than 4,500 g at delivery and have associated shoulder dystocia have significantly greater risks of injury noted at birth, injury persisting to hospital discharge, and Erb palsy. These associations are not singly due to birthweight, but are confounded by other factors, such as length of the second stage of labor.

Management of post-term pregnancy is directed toward timing and route of delivery. In the uncomplicated pregnancy, expectant management is customary up to 41 weeks’ gestation. Induction of labor, with or without cervical ripening measures, generally is done at the end of 41 weeks. Recent reviews show no increase in cesarean delivery among induced vs spontaneous labor patients, and studies do show a reduction in perinatal morbidity and cesarean delivery among low-risk mothers who are induced at or before 41 weeks. Unless the pregnancy is extended beyond 42 weeks, antepartum fetal surveillance generally is not recommended. Intrapartum surveillance is recommended in post-term labors, with special attention to amniotic fluid volume, meconium presence, progress of labor (due to risk of macrosomia), and fetal tolerance of labor.

References:


American Board of Pediatrics Content Specification(s):

Know the definition, risks to the fetus, and management of postterm pregnancy
A 25-year-old primigravida presents at 28 weeks' gestation with a complaint of decreased fetal movement. Her singleton pregnancy has been otherwise uncomplicated, and ultrasonography at 18 weeks' gestation revealed no abnormalities. Fetal growth has been adequate, and there is no evidence of premature rupture of membranes or preterm labor. A biophysical profile score of 6 out of 10 is obtained.

Of the following, the MOST appropriate course of action is:

1. daily nonstress tests
2. expectant obstetrical management
3. expeditious delivery of the fetus
4. repeated biophysical profile test at 32 weeks' gestation
5. repeated biophysical profile test in 6 to 24 hours

You selected 5, the correct answer is 5.

Do you want to add anything to your Learning Plan?
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The goal of antepartum fetal surveillance is to identify the compromised fetus and thereby reduce the risk of stillbirth, neonatal morbidity, and mortality. Fetal hypoxemia and acidosis alter the patterns and frequency of biophysical activities. Initially, asphyxia will cause loss of acute variables, such as heart rate reactivity, breathing, and movement. With chronic compromise and poor fetal renal perfusion, amniotic fluid production will be reduced.

Fetal well-being may be assessed using maternal perception of movement, cardiotocography (the monitoring of fetal heart rate and uterine contractions), and real-time ultrasonography. However, factors such as prematurity, fetal sleep-state, central nervous system abnormalities, and maternal medications (including corticosteroids) can alter fetal biophysical variables. Moreover, neither the degree nor the duration of fetal compromise can be identified precisely with antepartum testing, and little evidence exists to support the premise that the risk of fetal death can be reduced by such surveillance. Therefore, the indications for antepartum testing are considered relative, and include maternal and pregnancy-related conditions, in which the risk of stillbirth is increased, such as type 1 diabetes mellitus, hypertensive disorders, systemic lupus erythematosus, intrauterine growth restriction, isoimmunization, multiple gestation, oligohydramnios, and postterm pregnancy.

In the vignette, a biophysical profile test (BPP) was performed due to decreased...
fetal movement. The BPP was introduced in 1980 as a combined variable assessment of fetal well-being, and consists of a nonstress test (NST) combined with four observations made on ultrasonography (fetal breathing, movement, tone, and amniotic fluid volume). This assessment may be done as early as 26 weeks' gestation, with adjustment in interpretation for gestational age-appropriate behaviors. Likewise, the influence of the fetal sleep-state must be recognized, as both quiet sleep and asphyxia can depress biophysical activities. For each variable assessed with the BPP, a score of 0 (absent or abnormal) or 2 (present or normal) is given for a total of 10 possible points.

Components of the BPP

**NST.** The NST looks for fetal heart rate acceleration in association with fetal movement as an indicator of normal fetal autonomic function. A normal (reactive) NST demonstrates two or more fetal heart rate accelerations within a 20-minute period. Loss of reactivity occurs with a fetal sleep cycle and an assessment should be made for 40 minutes before the NST is considered abnormal. In addition, prematurity affects heart rate reactivity, with up to 50% of NSTs in fetuses less than 28 weeks' gestation being nonreactive. With the BPP, the NST may be omitted if all four components assessed by ultrasonography are normal.

**Fetal Breathing Movement (FBM).** Normal FBM as assessed with ultrasonography consists of intermittent, rhythmic episodes of diaphragm contraction, each lasting for more than a 30-second duration, within 30 minutes. With fetal asphyxia, loss of FBM occurs early and prior to loss of fetal movement. However, due to its episodic nature, FBM is the most frequently absent variable during normal BPP testing.

**Fetal Movement.** Normal fetal movement consists of four or more discrete body or limb movements within 30 minutes, and includes fine motor movement of the face and hands, as well as swallowing, sucking, yawning, kicking, rolling, and other purposeful movements.

**Fetal Tone.** Fetal tone is a very subjective measure and requires at least some movement of the fetus. A normal assessment consists of active extension with rapid return to flexion of a fetal extremity or opening and closing of a hand.

**Amniotic Fluid Volume.** Amniotic fluid is considered adequate if a single vertical pocket of amniotic fluid exceeds 2 cm.

The BPP is meant to assign a risk of fetal compromise, and to dictate management. A BPP score of 8 or 10 has a negative predictive value for fetal mortality exceeding 99%, and suggests continued routine surveillance and expectant obstetrical management of the pregnancy. A score of 6 is considered equivocal and raises concern, as fetal asphyxia cannot be ruled out. At term, a BPP of 6 should prompt delivery, while if preterm, BPP testing should be repeated in 6 to 24 hours. A score of 4 or less suggests that acute or chronic asphyxia is very likely and the fetus should be delivered. The relationship between a recent BPP and perinatal mortality is inverse and exponential. However, the positive predictive value is not well-studied, but felt to be quite poor. The false-positive rate for each technique for antenatal fetal testing is high and the development of management plans based on abnormal testing should always consider the gestational age, underlying fetal condition, the degree of oligohydramnios, and the maternal condition.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

References:

ACOG Practice Bulletin. Antepartum fetal surveillance. Number 9, October 1999


**American Board of Pediatrics Content Specification(s):**

Understand the rationale, interpretation, and shortcomings of the biophysical profile as a means of assessing fetal well-being.
A woman with an Rh (-) blood type is being followed up during pregnancy. Although this is her first pregnancy, her serum antiglobulin (anti-D) titer is 1:64 at 25 weeks' gestation. She has a history of emergent blood transfusion following a splenic laceration from a fall while waterskiing. Uterine size, fetal heart rate, and fetal movements are normal.

Of the following, the SAFEST technique available for effective estimation of the degree of fetal anemia is:

1. amniocentesis
2. cordocentesis
3. Doppler ultrasonography
4. fetal ascites assessment
5. serial maternal antibody titers

You selected 5, the correct answer is 3.

Do you want to add anything to your Learning Plan? (You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

Most Rh alloimmunization occurs following pregnancy, when the Rh(+) cells from the fetus sensitize an Rh(-) woman. If a subsequent fetus is also Rh(+), maternal antibodies (usually anti-D, anti-E, anti-c, or anti-Fy) enter the fetal circulation and induce hemolysis. In the primiparous, nonsensitized pregnant woman, sensitization is prevented by administration of antibody to the mother in the early part of the third trimester and after birth to remove fetal red blood cells from her circulation before she can mount an immune response. This technique is successful in 95% of cases. If the amount of antibody is insufficient to remove all of the transplacentally transferred fetal red blood cells, sensitization may occur. Also, women may become sensitized from blood transfusion of Rh(+) cells, which could potentially occur in emergent situations, such as described in this vignette.

Prenatal evaluation of the Rh(-) woman includes testing for alloimmunization. Once antibodies are detected, serial titers are performed. Should the maternal titer rise to 1:64 or higher, fetal assessment for anemia is indicated. Fetal anemia can develop as early as 17 weeks' gestation, requiring treatment in utero. Survival rates exceeding 90% may follow intrauterine transfusions in severely affected fetuses. Several techniques have evolved to evaluate for fetal anemia. Of these, the test that best combines diagnostic sensitivity with lowest risk for iatrogenic complications is Doppler ultrasonography.
The Rh blood type was described in the early 1940s, and its role in the pathogenesis of erythroblastosis fetalis was later identified. Maternal antibody titers were used to identify sensitized mothers. In the late 1940s, exchange transfusion was introduced to treat neonatal anemia, remove sensitized red blood cells from the fetal circulation, and lower bilirubin concentrations. This regimen allows for treatment of sensitized infants who are delivered late enough in pregnancy to avoid the lethal complications of prematurity. Because severe fetal anemia can occur as early as 17 weeks' gestation and fetal consequences increase with each sensitized pregnancy, neonatal treatment is unable to save some infants.

In Rh sensitization, antibody-coated red blood cells become hemolyzed with the resultant formation of bilirubin, which can be excreted by the mother. Bilirubin escapes into the amniotic fluid in proportion to the degree of hemolysis, and fluid obtained by amniocentesis can be analyzed based on the change of optical density (\(\text{-OD}\)) at a wavelength of 450 nm. Fetal risk can be predicted, and initially those fetuses at greatest risk could be delivered, admitted to intensive care, receive exchange transfusions, and hopefully, respond to treatment for their degrees of prematurity. Although amniocentesis is accurate and reliable, it carries the potential risks of fetal injury or loss, laceration of the placenta, stimulation of premature labor, infection, or worsening of sensitization.

Fetal anemia results in decreased blood viscosity, and compensatory increase in cardiac output results in high blood flow velocity. Doppler measurement of blood flow velocity in the middle cerebral artery (MCA) reliably correlates with the degree of anemia. Doppler measurements have been compared in a controlled manner with amniocentesis in the management of Rh alloimmunized pregnancies. Compared with the two commonly used methods for \(\text{-OD}\) analysis, Doppler measurements were similar in their ability to detect severe fetal anemia.

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
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</thead>
<tbody>
<tr>
<td>Doppler flow: MCA</td>
<td>88</td>
<td>82</td>
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<tr>
<td>(\text{-OD}:) Queenan graph</td>
<td>81</td>
<td>81</td>
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</tbody>
</table>

OD, optical density; MCA, middle cerebral artery.

* Adapted from Oepkes and associates (2006).

Although the Doppler MCA velocity is not perfect, its ability to detect severe fetal anemia without having to perform amniocentesis with similar sensitivity, specificity, and accuracy makes it the safer overall alternative. This technique should be performed by experienced sonographers; women with severe Rh alloimmunization require treatment in specialized referral centers. It is estimated that its use would decrease the use of invasive testing by half.

Cordocentesis is an accurate means of measuring fetal anemia, but it adds the risk of cord injury and bleeding to the existing risks of amniocentesis, making it less safe than Doppler MCA velocity.

Fetal ascites is a later finding of severe fetal anemia. Waiting for its presence places the fetus at added jeopardy, and it is not an accurate means of estimating fetal anemia. Ascites may interfere with the absorption of red blood cells from intrauterine transfusion into the abdominal cavity. Ultrasonographic measurements of the fetal liver and spleen have been evaluated and found to be less predictive of fetal anemia than are Doppler MCA velocities.

Do you want to add anything to your Learning Plan?
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References:


**American Board of Pediatrics Content Specification(s):**

Know how to diagnose and manage fetal-maternal blood group incompatibility and understand the potential complications and management

Know how to diagnose and manage fetal anemia and hydrops, including intrauterine transfusion
May: Question 7

You are counseling a 26-year-old woman with severe preeclampsia. This is her second pregnancy and she is at an estimated gestational age of 32 weeks. The woman is in her second year of medical school training and has many questions.

Of the following, the MOST accurate statement regarding preeclampsia is that:

1. A fetus is necessary for preeclampsia to develop.
2. Approximately 5% of pregnancies are affected by preeclampsia.
3. Endothelial function is normal in preeclampsia.
4. Normal trophoblast invasion of the spiral arteries characterizes placental histology in preeclampsia.
5. The woman's lifetime risk of cardiovascular death is similar to that of a woman who delivers prematurely without preeclampsia.

You selected 5, the correct answer is 2.

Do you want to add anything to your Learning Plan?
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Preeclampsia is a disease that is unique to pregnancy and affects approximately 5% of pregnant women. Women with preeclampsia are also found to have higher risks for long-term cardiovascular morbidity. For example, among women who deliver prematurely, those who have preeclampsia have an eightfold higher lifetime risk of cardiovascular death than those who do not have preeclampsia. Infants born to women with preeclampsia are also more likely than infants born to women without preeclampsia to have intrauterine growth restriction, interventional prematurity, and fetal death.

Some women have a higher risk of developing preeclampsia. Women with vascular disorders (such as chronic hypertension, diabetes, previous preeclampsia, and collagen vascular disease), multifetal pregnancies, and molar pregnancies have a three to fourfold increased risk for preeclampsia. Furthermore, preeclampsia resolves after delivery. The presence of abnormal vascular physiology, large placental mass, and resolution after birth suggests that preeclampsia is a systemic vascular disorder that is precipitated by placental and maternal interactions.

The pathophysiologic events that cause preeclampsia are yet to be fully elucidated. It is generally considered to be multifactorial in origin. Thus, although a number of theories on the pathogenesis of preeclampsia have been proposed, none have been confirmed.
A vasoactive mediator hypothesis proposes that altered systemic vascular tone and blood flow initiate a cascade of events that precipitates abnormal placental vascular development and infarction, hypertension, coagulopathy, proteinuria, edema, seizures, strokes, right upper quadrant pain (hepatic ischemia), and intrauterine growth restriction (Table).

### Table: Findings and Clinical Manifestations of Preeclampsia*

<table>
<thead>
<tr>
<th>System or Vasculature</th>
<th>Pathophysiology</th>
<th>Signs and Symptoms</th>
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</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Systemic vasoconstriction</td>
<td>Systemic hypertension</td>
</tr>
<tr>
<td></td>
<td>High cardiac output</td>
<td>Hemolysis</td>
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<tr>
<td></td>
<td>Increased hydrostatic pressure</td>
<td>Generalized edema</td>
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<td>Uterus and placenta</td>
<td>Uteroplacental insufficiency</td>
<td>Fetal growth restriction</td>
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<tr>
<td></td>
<td>Decidual ischemia and thrombosis</td>
<td>Fetal distress</td>
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<td></td>
<td></td>
<td>Abruptio placentae and placental infarcts</td>
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<tr>
<td>Renal</td>
<td>Decreased renal blood flow and glomerular filtration rate</td>
<td>Proteinuria</td>
</tr>
<tr>
<td></td>
<td>Endothelial injury</td>
<td>Renal insufficiency</td>
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<td></td>
<td>Angiotensin II hyperresponsiveness</td>
<td>Renal tubular necrosis and injury</td>
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<td>Ischemia</td>
<td>Seizures (eclampsia)</td>
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<td>Hemorrhage</td>
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<td>Regional ischemia</td>
<td>Coma</td>
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<td></td>
<td>Edema</td>
<td>Central blindness and loss of speech</td>
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<td>Liver</td>
<td>Ischemia</td>
<td>Elevated liver function tests</td>
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<td>Mitochondrial injury</td>
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<td>Hematologic</td>
<td>Hemolysis</td>
<td>Schistocytes and burr cells</td>
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<td></td>
<td>Decidual thrombosis and release of fibrin degradation products</td>
<td>High free hemoglobin and iron concentrations</td>
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<td>Low haptoglobin concentrations</td>
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<td>Thrombocytopenia, disseminated intravascular coagulation, and antiplatelet antibodies</td>
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</tbody>
</table>

* Adapted from Shah (2006).

A number of mediators have been investigated (such as angiotensin II, atrial natriuretic peptide, endothelin-1, neurokinin B, prostaglandins, thromboxanes, nitric oxide, and kallekreins).

Abnormalities in the renin-angiotensin system that may lead to preeclampsia have been supported by studies in transgenic mice, increased angiotensin responsiveness of the gravid uterine vasculature, hyperuricemia, renin gene overexpression in the gravid uterus, elevated renin concentrations in the uterus of women with preeclampsia, presence of autoantibodies to the angiotensin-1
receptor, and angiotensinogen mutations in some patient populations. Investigations of complementary mediators that are important in the pathogenesis of preeclampsia are ongoing.

A second theory about the cause of preeclampsia suggests that abnormal and blunted trophoblast invasion of the spiral arteries in uterine decidua and myometrium results in insufficient uteroplacental blood flow and hypoxic trophoblast tissue. Normally, extraembryonic trophoblastic stem cells originating in the blastocyst differentiate into the two functional and structural units of the placenta, the floating villus and the anchoring villus (Figure). This differentiation usually occurs by day 21 after ovulation.

Figure: Functional and structural units of the placenta.

The floating villus is composed of a monolayer of epithelial cells (cytotrophoblastic and syncytiotrophoblastic cells) that covers the entire surface of the villus and a central core composed of fetal vessels, fibroblasts, and macrophages. The syncytiotrophoblast is derived from cytotrophoblastic cells and is important for absorption, exchange, and endocrine functions and is the functional barrier between maternal blood and fetal stroma. The anchoring villus is composed of cytotrophoblastic cells that assume an "extravillous phenotype," detach from the basement membrane, and form columns that attach the floating villus to the uterus. Extravillous cytotrophoblasts also invade the uterine decidua, myometrium, and uterine spiral arterioles; remodel the endometrium; and form low-resistance, large-diameter blood vessels. This process is controlled by cytokines, growth factors, extracellular matrix components, oxygen tension, and hormones. Importantly, abnormal invasion of the uterine wall and its spiral arteries is characteristic of preeclampsia.

The uterine hypoxic state that occurs during preeclampsia induces trophoblast apoptosis, release of oxidants and microvilli of injured syncytiotrophoblast cells into the maternal circulation, and increased vascular resistance. The necessity for placental tissue and onset of preeclampsia after the 20th week of pregnancy supports the importance of abnormal placental development in the genesis of this disorder.

A third hypothesis about the origin of preeclampsia proposes that the increased cardiac output and blood flow that occurs normally during pregnancy injures end organs of genetically predisposed individuals. The vascular endothelium, uterus, kidney, liver, and brain subsequently are injured, resulting in the symptoms of
preeclampsia. A significantly higher risk of preeclampsia in daughters and not daughters-in-law of women with eclampsia supports a genetic susceptibility. Furthermore, similarities in the pathogenesis of preeclampsia and atherosclerosis (such as lipid profiles, insulin resistance, high serum iron concentration, and transferrin saturation) and presence of preexisting renal parenchymal or vascular disease in many women presenting with preeclampsia suggest that vascular injury, especially to the endothelium, in genetically at-risk women plays an important role in the pathogenesis of this disorder.

Other theories that have arisen from epidemiologic observations point to immunologic and genetic causes of preeclampsia. Primapaternity, or having a single male sex partner, has been implicated as an immune factor that contributes to the pathogenesis of preeclampsia. The duration for which a woman is exposed to paternal antigen from the same partner is inversely associated with the rate of preeclampsia. In addition, the risk for preeclampsia is higher with nulliparity, use of barrier contraception, and multiple sex partners. Several different genetic models for transmission have been suggested to contribute to a predisposition for preeclampsia. Autosomal recessive transmission, autosomal dominant transmission with variable penetrance, and a complex mode of inheritance that involves a combination of genetic and epigenetic phenomena have been proposed.

References:


Malassine A, Cronier L. Hormones and human trophoblast differentiation. Endocrine. 2002;19:3-11


Myatt L. Role of placenta in preeclampsia. Endocrine. 2002;19:103-111


American Board of Pediatrics Content Specification(s):

Know the morphologic structure of the placenta
You are meeting with a 23-year-old primigravida woman at 14 weeks' gestation. Her medical history includes having had successful repair for hypoplastic left heart syndrome. The woman and her husband, both nurses in the neonatal intensive care unit, are interested in understanding the physiologic changes during pregnancy that may affect the health of their fetus and the woman. You discuss the development and control of the uteroplacental circulation.

Of the following, the factor that is MOST important for control of blood flow to the uterus and placenta is:

1. blood volume
2. cardiac output
3. diastolic blood pressure
4. peripheral vascular resistance
5. regional autoregulation

You selected 3, the correct answer is 2.

Dramatic cardiovascular adaptations are required during pregnancy to produce an intrauterine environment conducive to fetal growth and development. Uterine blood flow increases 10-fold by the end of the pregnancy.

Cardiac output is the most important factor for uterine and placental perfusion during pregnancy. It increases approximately 20% by 8 weeks of gestation and then gradually increases by a maximum of 30% to 50% compared to prepregnancy levels. Increases in both heart rate (10% to 20%) and stroke volume (20% to 30%) contribute to the rise in cardiac output during pregnancy. The increase in cardiac output peaks between 25 and 30 weeks' gestation. Because myocardial oxygen demand rises and diastolic filling time diminishes with the changes in cardiac output, congestive heart failure, increased cyanosis, and reduced uteroplacental perfusion in women with cardiovascular disease often become clinically evident at this time during pregnancy. Although the mother in this vignette has a repaired hypoplastic left heart syndrome, cardiac output is dependent on the right ventricle which is not normally the systemic ventricle. It is unclear whether cardiac reserve will be sufficient in this clinical situation because few infants who have had successful repairs with the Norwood procedure have reached their childbearing years.
Cardiovascular diseases during pregnancy account for about 15% of perinatal deaths and 15% of preterm deliveries. Hypertensive disorders of pregnancy, chronic hypertension, preeclampsia, superimposed preeclampsia, eclampsia, and gestational hypertension comprise the majority of cardiovascular disease (5% to 8% of pregnancies). Intrauterine growth restriction most often occurs in association with hypertensive disorders with proteinuria (preeclampsia disorders, approximately 27% of infants weigh <2.5 kg at birth) and preterm birth (<37 weeks' gestation). The mechanism of growth restriction in preeclampsia is multifactorial but involves abnormal maternal hemodynamic adaptation and uterine hypoperfusion, placental insufficiency, endothelial dysfunction, aberrant fetoplacental growth signaling, and genetic/environmental factors. Of interest, infants of mothers with preeclampsia born after 37 weeks' gestation on average are larger than control infants.

Pre-existing vascular and congenital cardiac disorders affect about 1% of pregnancies. Fetal growth may be restricted in such pregnancies because of limited capacity to increase cardiac output and physiologic changes that worsen cyanosis by increasing right-to-left shunting in some cyanotic lesions. Intrauterine growth restriction occurs in 6% of pregnancies complicated by restrictive congenital lesions, such as valvular stenosis, coarctation, or cardiomyopathy. Cyanotic lesions, such as corrected transposition of the great arteries, are associated with a 25% incidence of fetal growth restriction if corrected and a 67% incidence if uncorrected. Furthermore, infants of women with congenital heart lesions have a 10-fold greater risk (8%-14%) of having congenital heart disease than the 0.8% rate found in all live births.

Renovascular disorders such as autoimmune diseases (ie, systemic lupus erythematosus and other rheumatologic disorders) may impair normal cardiovascular adaptation. Impaired fetal growth (40%), fetal loss, and preeclampsia (20%) may accompany this deficient cardiovascular adaptation.

Blood volume increases between 30% and 50% during pregnancy, which includes a rise in plasma volume of 45% to 60% and red cell volume of 25% to 32% by 32 weeks' gestation. The difference in plasma and red cell volumes largely contributes to the physiologic anemia of pregnancy. Total body water volume also increases significantly. These fluid volume changes occur because of arginine vasopressin release, renin-angiotensin-aldosterone system activation, and a change in the maternal osmolar set point. The presence of more body water does not cause strain on the normal gravid heart because (1) systemic and pulmonary vascular resistances are normally lower, (2) reserve cardiac capacity is usually greater than in abnormal hearts, and (3) uteroplacental capacity increases to accommodate the relative hypervolemia of the pregnant versus nonpregnant woman.

In the pregnant woman with unrepaired cyanotic congenital heart disease, Eisenmenger syndrome, New York Heart Association functional class 3 and 4, Marfan syndrome with aortic root diameter of 40 mm or more, or systemic ventricular ejection fraction of 40% or less, cardiac reserve and control of vascular resistance may limit the tolerance to these changes. Maternal congestive heart failure, arrhythmias, and, functional cardiac limitations may reduce uteroplacental blood flow. Limited cardiovascular adaptation may also result in fetal loss and intrauterine growth restriction.

During pregnancy, diastolic and systolic blood pressures decline to a nadir at the end of the second trimester. Diastolic pressure declines more than systolic pressure. By the end of the third trimester, both systolic and diastolic blood pressures will return to prepregnancy values. The normal decline in blood pressure is a response to a reduction in peripheral vascular resistance. If cardiac and vascular adaptation (ie, rise in cardiac output) is limited by congenital or acquired heart defects, uteroplacental blood flow may be compromised.
Blood flow to the uteroplacental circulation is normally driven by the maternal cardiac output. Adaptation of the uterus and placental growth occur during a normal pregnancy, blood flow is maximized by the development of low-resistance uteroplacental arteries (transformation of uterine spiral arteries), uterine angiogenesis throughout pregnancy, and refractoriness of uterine vasculature to vasoconstrictors. Essentially, autoregulation of uteroplacental blood flow is lost. Of note, the placentas of growth-restricted infants frequently maintain the ability for blood flow to be autoregulated by vasoconstrictor agents such as angiotensin II.

Do you want to add anything to your Learning Plan?
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References:


American Board of Pediatrics Content Specification(s):

Understand organ and integrated physiology of maternal adaptation to pregnancy and know the normal changes in physiologic variables and in laboratory values

Know the effect of maternal cardiac disease and its treatment on the fetus
A pregnant woman at 37 weeks' gestation notices fluid leaking from her vagina. She has no uterine contractions, fetal movement has not changed, and she experiences no fever, chills, or abdominal tenderness. Her physician asks her to come to the office to be evaluated.

Of the following, the test with the HIGHEST specificity and positive predictive value to evaluate for rupture of membranes is:

- fern testing of vaginal fluid
- nitrazine testing
- placental alpha microglobulin-1
- ultrasound evaluation
- visualization of cervix

You selected 3, the correct answer is 3.

Rupture of membranes (ROM) before the onset of labor is called premature rupture of membranes and occurs in approximately 8% of term gestations. When ROM is suspected, maternal evaluation should include confirmation of membrane rupture, gestational age, and fetal well-being.

Whether ROM occurs with a gush of fluid followed by continuous leakage or by otherwise unexplained wetness in the vaginal area, sterile speculum examination may demonstrate amniotic fluid flowing from the cervical os. If amniotic fluid is not leaking spontaneously, flow may be observed following a Valsalva maneuver or cough. Direct observation of amniotic fluid coming from the cervical os and pooling in the vagina is the most sensitive method to test for ROM. If amniotic fluid is observed, no additional evaluation is required. On the other hand, amniotic fluid may not be visualized on speculum examination if there is considerable delay between loss of amniotic fluid and examination; in this circumstance, results may be falsely negative.

Several tests have been devised to detect amniotic fluid in the vagina. Because amniotic fluid has a pH between 7 and 7.7, and the normal vaginal secretions are acidic, with pH ranging from 3.8 to 4.2, testing vaginal fluid with nitrazine paper yielding a blue result (pH >6.5) suggests ROM. False-positive results may occur due to soap, blood, semen, urinary tract infection with *Proteus* species, or vaginal infections such as *Trichomonas* or bacterial vaginosis.
When an amniotic fluid swab is placed on a glass slide and allowed to dry (10 minutes), a delicate arborization pattern is seen on the slide, known as “ferning.” On the other hand, dried cervical mucous usually results in a thick and wide arborization pattern; this pattern is seen with cervical mucous under the influence of estrogen.

A bedside slide test that uses immunochromatographic methods to detect trace amounts of placental alpha microglobulin-1 in the vagina is also useful for determining the presence of ruptured membranes. Although this test is as sensitive as other testing methods, its specificity is higher (ie, fewer false negatives) (Table).

<table>
<thead>
<tr>
<th>Nitrazine</th>
<th>Ferning</th>
<th>Placental alpha microglobulin-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity, %</td>
<td>97</td>
<td>96-99</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>99</td>
<td>96-98</td>
</tr>
<tr>
<td>Positive predictive value, %</td>
<td>99</td>
<td>98-99</td>
</tr>
<tr>
<td>Negative predictive value, %</td>
<td>96</td>
<td>90-99</td>
</tr>
</tbody>
</table>

Ultrasonographic determination of oligohydramnios or anhydramnios may be consistent with premature ROM, but is not sufficiently specific or sensitive to be considered diagnostic.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

References:


American Board of Pediatrics Content Specification(s):

Know the causes, complications, and management of premature rupture of membranes at greater than 36 weeks’ gestation

Know the causes, complications, and management of preterm premature rupture of membranes
A gravid woman presents for a routine prenatal visit. Her pregnancy has been uncomplicated, and is dated at 33 weeks' gestation based on last menstrual period and a first trimester ultrasound. However, at this visit her fundal height measurement falls short at 30 cm. Moderate hypertension is noted, and protein is found in her urine. She is referred for ultrasonographic evaluation of fetal well-being.

Of the following, the diagnosis of oligohydramnios for this patient is BEST supported by the ultrasonographic finding of:

1. a maximum vertical pocket measurement of less than 5 cm
2. a single vertical pocket measurement of less than 2 cm
3. an amniotic fluid index of less than 5 cm
4. an amniotic fluid index of less than 10 cm
5. "fetal crowding," as judged by the sonographer

You selected 5, the correct answer is 3.

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Oligohydramnios refers to a deficiency of amniotic fluid, and occurs in up to 8% of all pregnancies. The presence of oligohydramnios denotes potential fetal compromise, and is associated with increased rates of nonreactive nonstress tests, fetal heart rate decelerations, meconium staining, cesarean sections for fetal distress, low Apgar scores, and perinatal mortality. In addition, reduced amniotic fluid may be a marker for congenital malformations, aneuploidy, and growth restriction.

Amniotic fluid volume (AFV) varies according to gestational age, reaches an average of approximately 800 mL between 32 and 35 weeks' gestation, and decreases thereafter (Figure).

Figure: Nomogram showing amniotic fluid volume as a function of gestational age (From Gilbert [2006]).
Particularly during the third trimester, large variations in AFV exist among pregnancies, and within the same pregnancy on serial measurements. Direct measurement of AFV can be accomplished by amniocentesis with dye instillation, followed by repeated amniocentesis and calculation of dye-dilution. Using this technique, normative values for AFV based on gestational age have been constructed. Oligohydramnios can be defined by an AFV more than 2 standard deviations below the mean for a given gestational age.

Although less precise than dye-dilution, semiquantitative ultrasonographic techniques have been used as noninvasive methods for obtaining AFV measurements. A subjective assessment of AFV made by the sonographer is commonly used. This technique is limited by the experience of the sonographer to obtain an overall sense of fetal crowding, and when oligohydramnios is suspected, objective measurements are subsequently ascertained. Assessment of the maximum vertical pocket is one such objective measurement. The sonographer identifies the largest pocket of amniotic fluid, void of fetal parts or umbilical cord, and the vertical depth of this pocket is measured. Oligohydramnios is suggested if the largest single pocket measures less than 2 cm.

The most reproducible and valid method for ultrasonographic measurement of AFV is the amniotic fluid index (AFI). The AFI is the sum of the maximum fluid pockets, void of fetal parts or umbilical cord, in 4 equal quadrants of the uterus. Although dependent on gestational age, an AFI measurement between 10 and 24 cm after 30 weeks' gestation is considered within the normal range. Oligohydramnios is suggested if the AFI is lower than the fifth percentile for gestational age, and generally considered present if the AFI is less than 5 cm, regardless of gestational age.

Oligohydramnios generally results from rupture of membranes, absence of functioning renal tissue (congenital or secondary to obstructive uropathy), or reduced fetal urine production as a consequence of impaired uteroplacental flow. Diminished AFV is a clinical hallmark for fetal growth restriction, and oligohydramnios is frequently identified with the postterm pregnancy. An increased incidence of adverse perinatal outcomes has been associated with oligohydramnios, because of umbilical cord compression, uteroplacental insufficiency, and an increased incidence of meconium-stained fluid. As a result, in
the face of oligohydramnios at a gestational age of more than 37 weeks, the recommendation for delivery is almost uniform. However, isolated oligohydramnios may occur, in which maternal disease is absent, and the fetus is appropriately grown and exhibits reassuring well-being. Under these circumstances, perinatal outcomes may not be worsened and expectant management may be indicated.

Do you want to add anything to your Learning Plan?
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References:

American Board of Pediatrics Content Specification(s):
Know how to diagnose oligohydramnios, its significance, and the management of the pregnancy when it is diagnosed
A woman at 38 weeks’ gestation experiences a gush of fluid from her vagina. She has no contractions and otherwise feels well. She presents to her physician, who performs a sterile speculum examination revealing fluid flowing from the cervical os and pooling in the posterior fornix. Review of her medical records indicates that her gestational age by last menstrual period estimation was concordant with ultrasonography performed at 9 weeks’ gestation. Group B streptococcal screen was negative at 36 weeks’ gestation. Auscultation of the fetal heart rate indicates a steady rate at 136 beats per minute. Her first child was delivered vaginally 2 years ago after an uncomplicated pregnancy, labor, and delivery.

Of the following, the MOST appropriate next step would be to:

1. administer corticosteroids
2. induce labor with oxytocin
3. instill intrauterine indigo carmine
4. schedule cesarean delivery
5. start antibiotics

You selected 2, the correct answer is 2.

Do you want to add anything to your Learning Plan?
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At term, rupture of membranes (ROM) before the onset of labor occurs in about 10% of cases. Although the exact physiologic mechanism for ROM is not known, current understanding suggests roles for programmed cell death, activation of collagenases and other catabolic enzymes, and mechanical forces. Preterm ROM is thought to be due to early activation of one or more of these processes, possibly accelerated by inflammation or infection.

The management of rupture of membranes at any time in pregnancy involves three initial steps:

1. Confirmation of membrane rupture
2. Confirmation of gestational age
3. Assessment of fetal well-being

For these reasons, women with suspected ROM should seek prompt medical attention.

The diagnosis of ROM most assuredly is made by direct observation during sterile speculum examination of amniotic fluid pooling in the posterior fornix. With this finding, as in the vignette, ROM is adequately documented. If sufficient time has passed since ROM or if the flow is inadequate to document based on visual observation, presence of amniotic fluid in the vagina may be evaluated by testing vaginal secretions for ferning (fine arborization of dried fluid on a slide), alkaline
pH on nitrazine paper, or testing for placental alpha microglobulin-1 with a bedside immunochromatographic test. Abdominal ultrasonography to evaluate fluid volume also may be performed, even though low fluid volume is not specific for ROM. Among women with suspected preterm ROM, leakage of amniotic fluid into the vagina can be confirmed by instillation of indigo carmine into the uterus and evaluating for coloration on a vaginal tampon. For the woman in this vignette, no further testing to confirm membrane rupture is indicated.

Management of ROM varies with gestational age. Additional factors important for decision making include the presence of pregnancy complications (such as positive screening result for group B Streptococcus (GBS), Chlamydia infection, bacterial vaginosis, chorioamnionitis), pregnancy test results, and ultrasonographic and physical findings. For the woman in the vignette, early pregnancy findings and menstrual history confirm her to be at term.

Fetal well-being can be assessed by fetal heart rate and fetal ultrasound. With ROM, ultrasonography can be helpful in documenting reduced fluid volume (suggestive but not diagnostic for ROM) but is more useful in documenting fetal size, presentation, and position.

In the vignette, the pregnancy is at term with documented ROM and no signs of fetal compromise. The management of term ROM is to proceed to delivery. If cesarean section is being planned for other obstetric reasons, it should be done expeditiously; however, ROM without labor does not mandate cesarean delivery. Most women with ROM at term will go into labor and, without intervention, 70% will deliver within 24 hours and 85% will deliver within 48 hours.

Debate regarding the relative roles of expectant management versus induction of labor with oxytocin continues. In the vignette, initiation of oxytocin is the preferred option. The major risks for mother, fetus, and infant are associated with infection. The risk of infection increases with duration of ROM. For this reason, some physicians will recommend immediate induction. Others will observe for 12 to 24 hours for spontaneous onset of labor.

In any case, admission to the hospital after ROM is generally preferred. Compared with women hospitalized after ROM, women allowed to stay at home experienced greater use of antibiotics (odds ratio [OR] 1.52 [95% confidence interval (CI) 1.04-2.24]) and their infants had a higher incidence of neonatal infection (odds ratio 1.97 [95% CI 1.0-1.39]). A comparison of maternal and neonatal outcomes after induction with oxytocin versus expectant management is presented in the Table.
* Cesarean section after rupture of membranes without labor is more likely in primagravidas, in women experiencing labor for more than 12 hours, in women with previous cesarean delivery, and in women with epidural analgesia.

Among women who are at term, afebrile, and have a negative screening result for GBS, initiation of antibiotics is not recommended. Women who are culture positive for GBS should be treated according to national GBS guidelines. Use of antibiotics is frequently considered for preterm ROM when management goals include prolongation of pregnancy. Antibiotics were demonstrated to be helpful in prolonging pregnancy, reducing maternal infection, lowering rates of neonatal infection, reducing neonatal oxygen needs, and reducing the incidence of abnormal findings on cerebral ultrasonography. For the woman in the vignette, antibiotics would not be indicated at this time.

Antenatal corticosteroids are recommended in the presence of ROM for women at less than 32 weeks’ gestation who show no signs of infection. In the interval between 32 and 34 weeks’ gestation, corticosteroid use is controversial. Documentation of fetal lung immaturity may be useful in this circumstance. After 34 weeks’ gestation, corticosteroids are often avoided because of the risk of chorioamnionitis.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Induction With Oxytocin</th>
<th>Expectant Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal infection, %</td>
<td>4</td>
<td>8.6</td>
</tr>
<tr>
<td>Neonatal infection, %</td>
<td>2-3</td>
<td>2-3</td>
</tr>
<tr>
<td>Cesarean delivery, %</td>
<td>9.6</td>
<td>10.9*</td>
</tr>
<tr>
<td>Mothers’ satisfaction</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Chorioamnionitis, OR (95% CI)</td>
<td>0.74 (0.56-0.97)</td>
<td>1</td>
</tr>
<tr>
<td>Endometritis, OR (95% CI)</td>
<td>0.30 (0.12-0.74)</td>
<td>1</td>
</tr>
<tr>
<td>NICU admission, OR (95% CI)</td>
<td>0.72 (0.57-0.92)</td>
<td>1</td>
</tr>
</tbody>
</table>

CI = Confidence interval; NICU = neonatal intensive care unit; OR = odds ratio; and + and ++ = relative


Scorza WE. Management of premature rupture of the fetal membranes at term. UpToDate.com

American Board of Pediatrics Content Specification(s):
Know the causes, complications, and management of premature rupture of membranes at greater than 36 weeks’ gestation

Know the causes, complications, and management of preterm premature rupture of membranes
You are asked to provide consultation to a 43-year-old Caucasian gravida 1 para 0 woman who is pregnant and at 28 weeks' estimated gestational age. She has symptoms consistent with preeclampsia superimposed on chronic hypertension. On reviewing her chart you discover that she is carrying monozygotic twins and has smoked throughout her pregnancy.

Of the following, the risk factor that is MOST likely to reduce the risk of preeclampsia in the woman in the vignette is:

- advanced maternal age
- chronic hypertension
- cigarette smoking
- primigravid status
- twin gestation

You selected 1, the correct answer is 3.

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Preeclampsia refers to the onset of hypertension (systolic blood pressure [SBP] =140 mm Hg or diastolic blood pressure =90 mm Hg) and proteinuria (>300 mg protein in 24 hours, dipstick >1 +) after 20 weeks of gestation in a previously normotensive woman. Chronic hypertension (or preexisting hypertension) is defined as SBP greater than 140 mm Hg, diastolic blood pressure greater than 90 mm Hg, or both, that antedates pregnancy, is present before the 20th week of pregnancy, or persists longer than 12 weeks postpartum. Preeclampsia superimposed on chronic hypertension is diagnosed when a woman with preexisting hypertension develops new-onset proteinuria after 20 weeks of gestation. Women with both preexisting hypertension and proteinuria are considered preeclamptic if there is an exacerbation of blood pressure to the severe range (SBP >160 mm Hg or diastolic blood pressure >110 mm Hg) during the last half of pregnancy, especially if accompanied by symptoms, elevated liver enzymes, or thrombocytopenia.

Metaanalysis of clinical trials has shown that maternal cigarette smoking is associated with a significant reduction in the risk of preeclampsia (odds ratio [OR] 0.51, 95% confidence interval [CI] 0.37-0.63). This benefit does not outweigh the multiple medical risks associated with smoking during pregnancy such as:

- perinatal death
- low-birthweight birth
- preterm delivery
- placental abruption
- preterm premature rupture of membranes
- ectopic pregnancy
placenta previa

Despite the known harmful effects of smoking on the health of mothers and their children, it is estimated that 25% of American women of reproductive age smoke cigarettes. Oxygen delivery to the fetus is impaired in pregnant women who smoke. Pathologic studies of the placentas of women who smoke show structural changes, including a reduction in the fraction of capillary volume and increased thickness of the villous membrane, that are not seen in the placentas of nonsmoking women. Both of these factors may contribute to abnormal gas exchange within the placenta. Exposure to cigarette smoke also acutely decreases intervillous perfusion, possibly via nicotine-induced vasospasm. Animal models suggest that nicotine can also directly impair lung growth because of interaction with nicotinic acetylcholine receptors with resultant abnormal collagen accumulation. Carbon monoxide exposure from smoking causes the formation of carboxyhemoglobin, which has multiple effects on maternal and fetal oxygen delivery. Carboxyhemoglobin is a competitive inhibitor of oxyhemoglobin, clears slowly from the fetal circulation, and reduces tissue oxygenation by shifting the oxyhemoglobin dissociation curve to the left.

More than 2,500 substances are found in cigarette smoke, including ammonia, polycyclic aromatic hydrocarbons, hydrogen cyanide, vinyl chloride, nitrogen oxide, and carbon monoxide. Each of these substances could be responsible for adverse fetal and maternal outcomes in mothers who smoke. For example, term human infants with significant concentrations of cotinine, a by-product of nicotine metabolism, at delivery are limited in their ability to maximize and vary their heart rate during the first 4 hours after birth.

Advanced maternal age is an independent risk factor for preeclampsia (maternal age 40 years, relative risk [RR] 1.96, 95% CI 1.34-2.87). Older women also tend to have additional risk factors, such as diabetes mellitus and chronic hypertension.

There are many well-described risk factors for preeclampsia as illustrated in the Table.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced maternal age (≥40 y)</td>
<td>1.96</td>
<td>1.34-2.87</td>
</tr>
<tr>
<td>Chronic hypertension SBP ≥130 mm Hg</td>
<td>2.37</td>
<td>1.78-3.15</td>
</tr>
<tr>
<td>Chronic hypertension DBP ≥80 mm Hg</td>
<td>1.38</td>
<td>1.01-1.87</td>
</tr>
<tr>
<td>Twin gestation</td>
<td>2.93</td>
<td>2.04-4.21</td>
</tr>
<tr>
<td>Primigravid status</td>
<td>2.91</td>
<td>1.28-6.61</td>
</tr>
</tbody>
</table>

DBP = diastolic blood pressure; SBP = systolic blood pressure.

Preexisting hypertension, renal disease, and collagen vascular disease are well-described risk factors for preeclampsia. Multiple gestation increases the risk of preeclampsia. The first pregnancy in women carries a higher risk of developing preeclampsia than do subsequent pregnancies. It is unclear why the primigravid state is such an important predisposing factor.

Multiple gestation increases the risk of preeclampsia; for twin pregnancies the RR is 2.93, 95% CI 2.04-4.21. The first pregnancy in women carries a higher risk of developing preeclampsia than do subsequent pregnancies (RR 2.91, 95% CI 1.28-6.61).
References:


American Board of Pediatrics Content Specification(s):

Know the effects on the fetus of maternal chronic hypertension and its treatment

Know the effects on the fetus of mild preeclampsia and its management

Understand the probable gestational age at which teratogen exposure will produce common fetal anomalies

Know the effects on the fetus of maternal tobacco smoking
A 24-hour-old term infant is being evaluated for discharge. He was delivered by a 22-year-old primigravida African-American woman at 38 weeks’ gestation. His birthweight was 3,700 g. Maternal prenatal laboratory findings were normal. The plasma glucose concentration 1 hour after a 50-g glucose challenge test was 116 mg/dL (6.4 mmol/L). The infant has had no problems since birth. He is rooming in with the mother, is feeding well, and has voided and passed meconium. You are discussing the need for and optimal timing of screening for gestational diabetes mellitus (GDM) during this woman’s subsequent pregnancies.

Of the following, the BEST time for screening for glucose intolerance in this woman in association with her next pregnancy is:

- preconception
- 4 to 8 weeks
- 14 to 18 weeks
- 24 to 28 weeks
- not indicated

You selected [4], the correct answer is [4].

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Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. GDM complicates approximately 4% of all pregnancies in the United States, resulting in approximately 135,000 cases annually. The prevalence may range from 1% to 14% of pregnancies, depending on the population studied. GDM represents nearly 90% of all pregnancies complicated by diabetes.

Clinical recognition of GDM is important because factors such as dietary treatment, insulin, and antepartum fetal surveillance, can reduce GDM-associated perinatal morbidity and mortality. The timing of screening for GDM is important. Because maternal insulin resistance rises progressively during pregnancy, screening too early may miss some patients who will become glucose intolerant later. Screening too late in the third trimester may limit the time during which metabolic interventions can take place. Before 1997, screening for GDM was recommended in all pregnancies. Currently, the screening strategy for GDM is based on an assessment of risk for GDM determined at the first prenatal visit as outlined in Table 1. The woman in this vignette falls into the average-risk category because of her African-American race.

Table 1
The 50-g glucose challenge test (GCT) consists of administration of a 50-g oral glucose load followed by a plasma glucose determination 1 hour later. The patient need not be fasting. Various threshold levels for an abnormal 50-g glucose challenge are in use, including 140 mg/dL (7.8 mmol/L), 135 mg/dL (7.5 mmol/L), and 130 mg/dL (7.2 mmol/L). The sensitivity of the GDM testing regimen depends on the threshold value used. Pregnant women with a GCT result above the selected threshold require a diagnostic oral glucose tolerance test (OGTT). The most commonly used threshold, 140 mg/dL, detects only 80% of patients with GDM and necessitates a 3-hour OGTT in approximately 10% to 15% of patients. Using a challenge threshold of 135 mg/dL improves sensitivity to more than 90% but increases the number of 3-hour OGTTs by 42%.

The diagnostic OGTT is performed in the morning after an overnight fast of 8 to 14 hours after 3 days of unrestricted diet and physical activity. Either a 2-hour (75-g glucose) or a 3-hour (100-g glucose) test can be performed. The diagnostic criteria are shown in Table 2. Two or more values must be met or exceeded for the diagnosis of GDM to be made.

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Criteria</th>
<th>Screening Test</th>
<th>Screening Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>All criteria must be fulfilled</td>
<td>Not indicated</td>
<td>Not indicated</td>
</tr>
<tr>
<td></td>
<td>- Members of ethnic group with low prevalence of GDM</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- No known diabetes in first-degree relatives</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Age &lt;25 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Weight normal before pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- No history of abnormal glucose metabolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- No history of poor obstetric outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average risk</td>
<td>Members of an ethnic/racial groups with a high prevalence of diabetes (eg, Hispanic, Native American, Asian, African-American, Pacific islands, indigenous Australian ancestry)</td>
<td>One of the following:</td>
<td>24-28 wk</td>
</tr>
<tr>
<td></td>
<td>- Two step procedure: 50 g GCT followed by a diagnostic OGTT in those with abnormal GCT</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- One step procedure: diagnostic OGTT on all subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>- Maternal age &gt;25 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Previous infant &gt; 4 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Previous unexplained fetal demise</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Maternal obesity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Strong family history of type 2 diabetes or GDM</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Personal history of GDM</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Glucose intolerance</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Fasting glucose &gt;140 mg/dL (7.8 mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Random glucose &gt;200 mg/dL (11.1 mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Gastroesophageal reflux disease (GERD)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The diagnostic OGTT is performed in the morning after an overnight fast of 8 to 14 hours after 3 days of unrestricted diet and physical activity. Either a 2-hour (75-g glucose) or a 3-hour (100-g glucose) test can be performed. The diagnostic criteria are shown in Table 2. Two or more values must be met or exceeded for the diagnosis of GDM to be made.

<table>
<thead>
<tr>
<th>Fasting Value</th>
<th>With 100-g Glucose Load, mg/dL (mmol/L)</th>
<th>With 75-g Glucose Load, mg/dL (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 h</td>
<td>180 (10.0)</td>
<td>155 (8.6)</td>
</tr>
<tr>
<td>2 h</td>
<td>155 (8.6)</td>
<td>155 (8.6)</td>
</tr>
<tr>
<td>3 h</td>
<td>140 (7.8)</td>
<td>--</td>
</tr>
</tbody>
</table>

* Adapted from Chimaik and Moore (2005)
References:


American Board of Pediatrics Content Specification(s):

Know the rationale and methods for screening for glucose intolerance during pregnancy
A 26-year old primiparous woman presents with labor at 24 weeks' gestation. On speculum examination, a fully-effaced cervix is dilated 2 cm. No fluid is noted to come from the cervical os. To provide time for antenatal corticosteroid effect, tocolytic therapy is being discussed.

Of the following, the tocolytic agent that exerts its effect through blockade of myometrial contractile stimulants is:

1. beta-adrenergic receptor agonist
2. calcium channel blocker
3. magnesium sulfate
4. nitric oxide donor
5. prostaglandin synthesis inhibitor

You selected 5, the correct answer is 5.

Preterm labor (PTL) is defined as labor occurring after 20 weeks' but before 37 weeks' gestation. It is defined by the presence of regular uterine contractions at frequent intervals associated with cervical effacement (>80%) or dilatation (at least 2 cm). Generally, more than four contractions per hour are needed to cause cervical change. Preterm birth complicates 10% to 15% of all pregnancies. It is the commonest cause of neonatal morbidity and mortality, and causes 75% of neonatal deaths that are not associated with congenital anomalies. Therefore efforts to prevent or inhibit PTL are warranted.

Decisions about management of PTL are made based on estimated gestational age (less than 34 to 36 weeks' gestation), estimated weight of the fetus (<2,500 g), and presence of contraindications to tocolysis (Table 1).

Table 1
A number of drugs and other interventions have been used to prevent or inhibit preterm labor; none has been very effective. Because of uncertainty about progression of labor despite tocolytic medications, the American College of Obstetricians and Gynecologists has recommended that tocolysis may be considered when uterine contractions are regular and the changes in cervical dilatation and effacement are appreciable.

Tocolytic agents in current use inhibit myometrial contractions but do not affect the primary stimulus for preterm labor. Tocolytics function through one of two mechanisms, alteration of intracellular metabolic pathways or blockade of myometrial contractile stimulants. Intracellular messaging is altered by B-adrenergic receptor agonists (ritodrine, terbutaline), nitric oxide donors (nitroglycerin), magnesium sulfate, and calcium-channel blockers (nifedipine). Agents that inhibit the synthesis or action of myometrial contractile stimulants include prostaglandin-synthesis inhibitors (indomethacin) and oxytocin antagonists (atosiban).

The decision to use a specific tocolytic agent should be carefully considered because of the side effects associated with each agent (Table 2).

Table 2

<table>
<thead>
<tr>
<th>Maternal Factors</th>
<th>Fetal Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe hypertensive disease</td>
<td>Fetal death or lethal anomaly</td>
</tr>
<tr>
<td>• exacerbation of chronic hypertension</td>
<td>Fetal distress</td>
</tr>
<tr>
<td>• eclampsia</td>
<td>Intrauterine infection (chorioamnionitis)</td>
</tr>
<tr>
<td>• severe preeclampsia</td>
<td>Therapy adversely affecting the fetus (e.g., fetal distress because of attempted suppression of labor)</td>
</tr>
<tr>
<td>Pulmonary or cardiac disease</td>
<td>Estimated fetal weight ≥ 2500 g</td>
</tr>
<tr>
<td>• pulmonary edema</td>
<td>Erythroblastosis fetalis</td>
</tr>
<tr>
<td>• adult respiratory distress syndrome</td>
<td>Severe intrauterine growth restriction</td>
</tr>
<tr>
<td>• valvular disease</td>
<td></td>
</tr>
<tr>
<td>• tachycardia</td>
<td></td>
</tr>
<tr>
<td>Advanced cervical dilatation (&gt; 4 cm)</td>
<td></td>
</tr>
<tr>
<td>Maternal hemorrhage</td>
<td></td>
</tr>
<tr>
<td>• abruptio placentae</td>
<td></td>
</tr>
<tr>
<td>• placenta previa</td>
<td></td>
</tr>
<tr>
<td>• disseminated intravascular coagulation</td>
<td></td>
</tr>
</tbody>
</table>

* Adapted from Roman and Pernoll (2007).
The use of multiple tocolytic agents simultaneously may have an additive effect but also increases the risk of serious side effects.

Prostaglandin synthase (cyclooxygenase, COX) is responsible for converting arachidonic acid to prostaglandin H₂. Such prostaglandins are important for stimulating changes in myometrial gap junctions and intracellular calcium signaling that occur during labor. COX-1 is an isoform of prostaglandin.
synthase constitutively expressed in the myometrium, decidua, and fetal membranes. COX-2 is an inducible isoform that increases in the decidua and myometrium during labor, both term and preterm. Indomethacin is a nonspecific COX inhibitor that reduces prostaglandin production, and is the most commonly used agent for inhibiting preterm labor. Newer COX-2 inhibitors, such as nimesulide, are under investigation. Maternal side effects associated with prostaglandin synthase inhibitors may include gastrointestinal bleeding, blood pressure elevation, and coagulation disturbances (Table 2). Fetal and neonatal side effects may include renal effects and reduction in amniotic fluid volume. With prolonged use, generally defined as longer than 48 hours, the ductus arteriosus may close and cause fetal and neonatal pulmonary hypertension, a risk pertinent to the case in the vignette.

B-adrenergic-receptor agonists increase the intracellular concentration of cyclic AMP, an activator of protein kinase. Protein kinase inhibits myosin light-chain kinase, thereby inhibiting myometrial contraction. A metaanalysis of several studies has demonstrated a reduction in preterm birth within 48 hours after treatment, but this effect is not detectable at 7 days. No effect on perinatal morbidity and mortality was found. Maternal side effects may be significant, especially pulmonary edema and arrhythmias (Table 2). Fetal and neonatal side effects may include tachycardia, fetal hyperglycemia, neonatal hypoglycemia, and myocardial ischemia.

Nitric oxide donors, such as nitroglycerin, have not been extensively used for prevention of preterm labor. Nitric oxide vasodilates smooth muscle cells within the uterus by activating guanylyl cyclase that induces cyclic GMP production. Myosin light-chain kinases are inactivated and muscle relaxation occurs. Small randomized trials and case studies involving acute uterine relaxation indicate that nitric oxide donors may be beneficial, although additional study is necessary. Maternal side effects include flushing, hypotension, and dizziness; information about fetal and neonatal side effects from maternal administration is limited (Table 2).

Magnesium sulfate decreases the intracellular concentration of calcium in myometrial cells, thereby inducing relaxation. Although widely used, efficacy in prolonging labor is yet to be clearly established. Maternal side effects may include diplopia, hypotension, muscle weakness, and pulmonary edema (Table 2). Fetal and neonatal side effects may include hypotonia and respiratory depression.

Calcium channel blockers directly inhibit the intracellular influx of calcium and release of calcium from the endoplasmic reticulum, both important for muscle contraction. Nifedipine is the agent most often used, however, no placebo-controlled trials have been reported. Therefore, evidence for safety and efficacy is limited. Maternal side effects associated with calcium channel blockers may include hypotension, nausea, tachycardia, and dizziness (Table 2). Fetal and neonatal side effects may include sudden fetal death, tachycardia, hypotension, and fetal distress.

Oxytocin receptor antagonists such as atosiban block the action of oxytocin on inositol triphosphate–induced release of intracellular calcium. A metaanalysis of atosiban studies found that atosiban was associated with an excess of fetal and infant deaths when given before 28 weeks’ gestation. Atosiban or other oxytocin receptor antagonists have not been approved for use in the United States. Potential maternal side effects may include nausea and headache (Table 2). Fetal bradycardia and fetal distress have been reported with atosiban (Table 2).

Most placebo-controlled trials of tocolytic medications are underpowered to evaluate the outcomes. Overall, however, women who received any tocolytic agent had a mean time to delivery of approximately 48 hours. Although tocolytic agents are widely used in North America and Europe, several are not approved by the US Food and Drug Administration for this indication (terbutaline, atosiban); conversely, ritodrine is approved for tocolysis of preterm labor but is no longer available for use in the United States. Atosiban, an inhibitor of oxytocin, is the first-line tocolytic agent in Europe.

Although the efficacy of tocolysis has been much debated, it is generally accepted that a 48-hour delay in delivery may facilitate maternal transport and fetal lung maturation after administration of corticosteroids. Tocolytic therapy should be considered in the patient with cervical dilatation less than 5 cm. Successful tocolysis is generally defined by fewer than 4 to 6 uterine contractions per hour without further cervical change. The short-term goal of tocolysis is to continue the pregnancy for 48 hours after corticosteroid administration, the duration of time generally needed to have a maximum
effect. The long-term goal is to continue the pregnancy beyond 34 to 36 weeks' gestation (depending on the institution), at which time fetal morbidity and mortality are significantly reduced and tocolysis can be discontinued. Long-term tocolysis is controversial because of side effects on the mother and infant (Table 2).

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

References:


American Board of Pediatrics Content Specification(s):

Know the effects of tocolytic agents used during pregnancy
May: Question 7

A 6-day-old, 35-week-gestation daughter of the Director for the Centers for Medicare and Medicaid Services is ready for discharge home. She had transient hypothermia and tachypnea after birth that prompted admission to the neonatal intensive care unit. Breast feedings, although slow, are coordinated and her weight is increasing. She appears well, other than being icteric, and is physiologically stable. You are discussing the infant’s medical issues during the hospitalization, outcomes, and the costs of infants born late preterm.

Of the following, late preterm infants in the United States are:

1. decreasing as a percentage of all live births
2. less likely to have difficulties in school than term infants
3. physiologically as mature as term infants
4. rehospitalized less frequently than infants born more preterm
5. the largest subpopulation of preterm live births

You selected 5, the correct answer is 5.

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Late preterm infants are born at 34 0/7 weeks’ gestation to 36 6/7 weeks’ gestation (Figure 1).

Figure 1: Late preterm definition. (Adapted from Raju et al [2005].)

The term late preterm has replaced the use of “near term” because it more accurately reflects the risks associated with birth at this range of gestational ages. This subgroup of preterm infants accounts for 71% of all live preterm births (2002), the largest subgroup of preterm births. As a group, the birth rate of late preterm infants is growing more rapidly than all other populations of infants except those born at term (Table 1). Between 1992 and 2002, the rate of increase in late preterm live births was 14.3%, compared with a rate of 20.9% in term infants. The rate of increase in infants born at 40 weeks’ gestation (-10.6%) and postterm (-30.5%) has declined such that the median gestational age at birth is now 39 weeks.

Table 1
Late preterm infants, such as the infant in this vignette, are mistakenly thought to be physiologically as mature as term infants. For example, the weight of the brain of a 34 weeks' gestation infant is only two thirds (Figure 2) and myelination is only one third that of term infants.

Figure 2: Brain weight versus gestational age. (Adapted from Kinney [2006].)

The finding that late preterm infants as a group do less well in school than term counterparts suggests that neuronal maturation and catch-up brain growth may be delayed or incomplete (Table 2).

### Table 1. Gestational Age-Specific Births (All Singleton Live Births), United States*

<table>
<thead>
<tr>
<th>Gestational Age, wk</th>
<th>1992, %</th>
<th>1997, %</th>
<th>2002, %</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 32</td>
<td>1.5</td>
<td>1.4</td>
<td>1.4</td>
<td>-8.7</td>
</tr>
<tr>
<td>32-34</td>
<td>2.5</td>
<td>2.5</td>
<td>2.6</td>
<td>+4.0</td>
</tr>
<tr>
<td>35-36</td>
<td>5.6</td>
<td>6.0</td>
<td>6.4</td>
<td>+14.3</td>
</tr>
<tr>
<td>37-39</td>
<td>42.1</td>
<td>47.5</td>
<td>52.1</td>
<td>+20.9</td>
</tr>
<tr>
<td>40</td>
<td>23.6</td>
<td>23.0</td>
<td>21.1</td>
<td>-10.6</td>
</tr>
<tr>
<td>41-44</td>
<td>23.6</td>
<td>19.5</td>
<td>16.4</td>
<td>-30.1</td>
</tr>
</tbody>
</table>

Glucuronyltransferase activity at birth is about half that of term infants and accounts for a greater propensity for jaundice (Figure 3).

Furthermore, apnea associated with deglutition and incoordination of oromotor function of late preterm infants contributes to feeding problems. Feeding problems may be masked during the birth hospitalization, especially if breastfeeding, because the infant is not challenged with an adequate volume of milk for several days. This often occurs several days after discharge home. Poor oral intake and low activity of bilirubin enzymes further contribute to the development of jaundice several days after birth.

Complications of preterm birth reflect physiologic immaturity in late preterm infants and result in more frequent admission to neonatal intensive care units than term infants. Common problems include temperature instability, hypoglycemia, need for intravenous fluid administration, respiratory distress, and jaundice (Figure 4).
After discharge from the birth hospitalization, late preterm infants are readmitted more than two to three times as often as term infants. The most frequent reasons are jaundice or possible infection. It appears that late preterm infants born to primiparous mothers who have had complications during the pregnancy, are breastfeeding, and are of Asian–Pacific Islander descent have higher rates of readmission (Table 3).

Table 3

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Morbidity, %</th>
<th>Adjusted RR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primiparous</td>
<td>7.1</td>
<td>1.3</td>
<td>1.2, 1.7</td>
</tr>
<tr>
<td>Asian/Pacific Islanders</td>
<td>2.1</td>
<td>1.3</td>
<td>1.0, 1.7</td>
</tr>
<tr>
<td>Labor/delivery complications&gt;1</td>
<td>7.1</td>
<td>1.3</td>
<td>1.1, 1.5</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>7.1</td>
<td>1.7</td>
<td>1.4, 2.1</td>
</tr>
</tbody>
</table>

CI = confidence interval; RR = relative risk

Of all infants born before 36 weeks of gestation and readmitted to the hospital, infants born at 34 and 35 weeks’ gestation account for about 55% of the readmissions, 45% of readmission hospital days, and 42% of the total costs of hospital readmissions because of the relatively greater number of births (Table 4).

Table 4

<table>
<thead>
<tr>
<th>Gestational Age, wk</th>
<th>No. (%)*</th>
<th>No. of Readmissions (% total)</th>
<th>% Infants Readmitted</th>
<th>No. of Readmissions (% total)</th>
<th>No. of Hospital Days (% Total)</th>
<th>Average Hospital Days</th>
<th>Cost, Millions $ (% Total)</th>
<th>Cost per Admission, $</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤33</td>
<td>101,362</td>
<td>(28)</td>
<td>15</td>
<td>24,959 (48)</td>
<td>115,648 (55)</td>
<td>8.8†</td>
<td>212.8 (25)</td>
<td>8,510</td>
</tr>
<tr>
<td>34–35</td>
<td>162,521</td>
<td>(47)</td>
<td>13</td>
<td>26,739 (52)</td>
<td>111,835 (45)</td>
<td>5.6</td>
<td>157.2 (43)</td>
<td>5,830</td>
</tr>
<tr>
<td>Total</td>
<td>263,883</td>
<td>38,685</td>
<td>15</td>
<td>51,798 (52)</td>
<td>227,483 (45)</td>
<td>6.4</td>
<td>370.0 (43)</td>
<td>7,151</td>
</tr>
</tbody>
</table>

* Adapted from Underwood MA, Danilek-B, Gilbert WM. J Perinatol. 2007 27:614-619
† 14.5 days at 33 weeks’ gestation to 31% at <25 weeks’ gestation
‡ 6.5 days at 33 weeks’ gestation to 12.2 days at <25 weeks’ gestation

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References:
Engle WA. A recommendation for the definition of “late-preterm” (near-term) and the birth weight-gestational age classification system. *Semin Perinatol*. 2006;30:2-7


**American Board of Pediatrics Content Specification(s):**

Identify perinatal risk factors, including hypoxic ischemic encephalopathy and prematurity, which affect subsequent developmental outcome

Know the type and frequency of school-related and behavior problems in preterm infants
Studies of the process of normal labor and of the pathophysiology of preterm labor suggest that human parturition is regulated by a distinctly human sequence of events. Preterm birth affects 5% to 15% of pregnancies and 70% of neonatal deaths are associated with birth occurring at gestations of 37 weeks or less, making understanding this process essential if effective strategies to prevent preterm labor are to be found.

Of the following, the process MOST uniquely associated with the onset of labor in humans is:

1. dissolution of the maternal corpus luteum
2. fall of maternal circulating progesterone
3. placental expression of corticotropin-releasing gene
4. release of fetal fibronectin into the cervix
5. spontaneous upregulation of the fetal hypothalamic-adrenal axis

You selected 4, the correct answer is 3.

Do you want to add anything to your Learning Plan?
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Unique to humans, timing of labor and birth is regulated through placental expression of the gene for corticotropin-releasing hormone (CRH). In humans and in great apes, CRH concentrations rise throughout pregnancy and peak at the time of delivery. Labor and delivery follow a period of exponential rise of CRH associated with a simultaneous decrease in concentration of CRH-binding protein. CRH receptors have been identified in maternal and fetal pituitary and adrenal glands. In addition, myometrial tissue in the mother and lung tissue in the fetus have CRH-binding sites.

Increases in CRH concentrations and bioavailability result in release of corticotropin by the maternal and fetal pituitary glands and secretion of cortisol by the maternal and fetal adrenal glands. Cortisol, whether secreted by the fetus or received from the mother, further stimulates the expression of the CRH gene by the placenta, causing added CRH secretion through this positive feedback system.

The rate of increase of CRH is considered to be the critical variable and the most accurate predictor of onset of labor. When comparing pregnancies at similar gestation, large differences in absolute CRH concentration are noted. Therefore individual CRH concentrations have a low sensitivity in predicting onset of labor.

Following the secretion of CRH and increased cortisol concentrations, a number of other events facilitate the process of parturition:

- Myometrial CRH receptors change from a form facilitating relaxation of myometrial cells into a form linked to activate contraction.
Oxytocin and prostaglandin F2 alpha are potentiated.
- Maternal and fetal adrenal glands produce dehydroepiandrosterone sulfate, a substrate for placental estrogens which stimulate uterine contractions.
- Surfactant and surfactant protein is synthesized and released into the amniotic fluid.
- Proinflammatory effects of prostaglandins and macrophages are stimulated by surfactants and surfactant protein A.
- Prostaglandin H2 synthetases in the chorion and amnion are activated.
- Cyclooxygenase-2 (COX-2) activity increases, which raises the concentration of prostaglandin E2, which becomes more proinflammatory as chorionic prostaglandin dehydrogenase synthesis decreases.
- Prostaglandin-mediated release of metalloproteinases weakens the membranes.
- Breakdown of the junction between the fetal membranes and decidua caused by inflammatory infiltrates and metalloproteinases results in the release of the adhesive protein fetal fibronectin into vaginal fluids.

Labor is also associated with changes in the myometrium needed to progress from growth accommodation (distention not producing contraction) to progressive, stronger contractions sufficient to produce birth. Three processes that enhance contractions have been identified:

- Promotion of myocyte contractility through enhancement of actin-myosin interactivity as CRH receptors in the myometrium change from the inhibitory form (BRHR1alpha) to a form stimulating the Galphaq contractile pathways.
- Increase in the excitability of myometrial cells associated with decline in the activity of beta2 and beta3 sympathomimetic receptors that function to open potassium channels and suppress contractility.
- Promotion of synchrony of myometrial cell contractions through the actions of connexin 43, prostaglandin F2alpha, and calcium.

Progesterone withdrawal is associated with a change from growth accommodation to stretch-induced contraction. In contrast to the process in many mammals, in humans, progesterone concentrations do not fall at the onset of labor. A functional withdrawal of progesterone activity accompanies modifications of the progesterone receptors A, B, and C. Decreases in several progesterone receptor coactivators result in reduced biologic activity of progesterone in the human at the onset of labor. The progesterone antagonist RU486 will initiate labor at any time during pregnancy.

Although inflammation has a major role in CRH initiation of labor, primary inflammation may initiate labor and do so without an increase in CRH. This effect may be mediated through factors such as COX-2 or interleukin-8.

In humans, the functions of the corpus luteum are assumed by the placenta early in pregnancy. Parturition in goats is dependent on dissolution of the maternal corpus luteum.

Although sheep are used for a number of perinatal physiological studies, parturition in sheep is dependent on processes initiated by the fetal hypothalamus, pituitary, and adrenal glands.

Human birth is a unique and complicated process. Understanding preterm birth may be enhanced with increased knowledge of the physiologic effects of the many epidemiologic factors related to preterm birth.

Do you want to add anything to your Learning Plan?
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References:

**American Board of Pediatrics Content Specification(s):**

Understand the physiological and molecular biological characteristics of normal labor
A pregnant woman at 39 weeks’ gestation feels uterine contractions every 4 minutes. As you wait for the delivery, you are reviewing with the obstetrician the hormonal responses during labor.

Of the following, induction of labor in this woman is MOST likely to occur by suppressing the function of:

1. corticotropin-releasing hormone
2. estrogen
3. oxytocin
4. progesterone
5. prostaglandins

You selected 5, the correct answer is 4.

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During parturition, the uterus must change from a relaxed to a powerful rhythmic contractile muscle. Removal of mechanisms that maintain uterine quiescence and recruitment of factors that promote uterine contractility mediate this transition. As the fetus grows and uterine enlargement ceases at the end of the third trimester, the increasing tension on the uterine wall also contributes to the onset of parturition. In addition, inflammatory cytokines entering the cervix and metalloproteases degrading the cervical collagen contribute to cervical ripening. Understanding the complex pathways involved in human parturition has been complicated by a lack of an animal model, because animals have significant mechanistic differences of labor compared with humans. Indeed, we are only recently beginning to understand the intricate hormonal influences on human labor. The precise molecular signals that trigger these hormonal changes are still unknown, but are probably mediated by fetal, placental, and maternal pathways.

During pregnancy progesterone maintains the uterus in a relaxed state. A withdrawal of progesterone function is essential for inducing labor in the woman in this vignette. Because circulating progesterone concentrations remain stable during labor, the functional suppression of progesterone is probably mediated by decreases in progesterone receptors as labor begins. In addition, progesterone receptor coactivators decrease with the onset of labor, perhaps further attenuating progesterone function. By limiting progesterone function, uterine myocyte attachment to the intercellular matrix increases, leading to an activation of mitogen-associated protein kinases and uterine contractility. The consequence of progesterone withdrawal is evident by the effect of administering the progesterone antagonist mifepristone, also known as RU-486, which can induce labor at any
time during pregnancy.

Increasing maternal plasma corticotropin-releasing hormone (CRH) concentrations are strongly associated with the timing of delivery; CRH concentrations increase exponentially with advancing gestation and peak at the time of delivery. CRH is produced by the placenta and incites the maternal and fetal pituitary glands to release corticotropin, leading to the release of cortisol from the maternal and fetal adrenal glands. Increased cortisol concentrations stimulate further CRH production by the placenta; this continuous positive feedback creates an exponential rise in CRH production. Cumulatively, these hormonal increases lead to fetal lung maturation and a change in amniotic fluid proteins, phospholipids, and myometrial receptor expression, which help to precipitate labor and delivery. In addition, CRH influences other hormones involved in parturition by enhancing the estrogen effects on the uterus; increasing prostaglandin production by the amnion, chorion, and decidua; and potentiating the oxytocin effect on the uterus.

Estrogens contribute to human parturition by increasing the strength of uterine contractions. This effect is mediated by estrogen-induced upregulation of myometrial gap junctions and uterotonic receptors. Not surprisingly, circulating maternal estrogen concentrations increase before the onset of labor.

Oxytocin is a potent inducer of uterine contractility. While maternal serum oxytocin concentrations remain stable during parturition, uterine oxytocin receptors increase 300-fold. Evidence suggests that the effects of oxytocin may be mediated by increased myometrial calcium and/or a greater sensitivity of the myometrium to intracellular calcium. In addition, in vitro data suggest that oxytocin stimulates the production of prostaglandin F2a, leading to further myometrial contractility.

Concentrations of E and F prostaglandins in amniotic fluid and maternal plasma and urine increase before the onset of labor. Prostaglandins play a central role in synchronizing uterine contractions, ripening the cervix, and increasing the myometrial sensitivity to oxytocin. Whereas prostaglandin F2a is thought to be important in initiating uterine contractility, prostaglandin E2 seems to play an important role in cervical ripening and rupture of fetal membranes.

References:


American Board of Pediatrics Content Specification(s):

Understand the physiologic and molecular biological characteristics of normal parturition

Understand the physiological and molecular biological characteristics of normal labor
Understand the effects of normal labor on uteroplacental physiology and its effects on the fetus
A 24-year-old primiparous woman is undergoing prenatal assessment at an estimated gestational age of 30 weeks. The amniotic fluid index, measured ultrasonographically, is estimated at 3.0 cm, suggestive of oligohydramnios. There is no history of preterm rupture of membranes and prolonged leakage of amniotic fluid. You are discussing with medical students the factors that contribute to amniotic fluid volume during pregnancy.

Of the following, the LARGEST contributor to amniotic fluid volume at 30 weeks' gestational age is fetal:

- lung liquid synthesis
- membrane fluid flux
- oral/nasal secretion
- swallowing
- urine production

You selected 5, the correct answer is 3.

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During the course of normal gestation, the amniotic fluid volume increases steadily from an estimated average of 65 mL at 12 weeks, reaches a peak average of 835 mL at 32 weeks, and decreases thereafter to an average of 500 mL at 42 weeks (Table).

<table>
<thead>
<tr>
<th>Gestational Age, wk</th>
<th>50th Percentile, mL</th>
<th>5th Percentile, mL</th>
<th>95th Percentile, mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>65</td>
<td>20</td>
<td>125</td>
</tr>
<tr>
<td>16</td>
<td>170</td>
<td>85</td>
<td>420</td>
</tr>
<tr>
<td>20</td>
<td>375</td>
<td>170</td>
<td>750</td>
</tr>
<tr>
<td>24</td>
<td>585</td>
<td>250</td>
<td>1290</td>
</tr>
<tr>
<td>28</td>
<td>750</td>
<td>335</td>
<td>1670</td>
</tr>
<tr>
<td>32</td>
<td>835</td>
<td>420</td>
<td>1880</td>
</tr>
<tr>
<td>36</td>
<td>930</td>
<td>375</td>
<td>1750</td>
</tr>
<tr>
<td>40</td>
<td>625</td>
<td>290</td>
<td>1420</td>
</tr>
<tr>
<td>42</td>
<td>500</td>
<td>250</td>
<td>1130</td>
</tr>
</tbody>
</table>

*Adapted from Brack and Wolf (1989).

Oligohydramnios is diagnosed when the amniotic fluid volume is less than 45% of the mean volume for any given gestational age. Similarly, polyhydramnios is diagnosed when the amniotic fluid volume is greater than 220% of the mean volume for any given gestational age. Alternatively, oligohydramnios and polyhydramnios may be diagnosed using absolute cutoff limits for the amniotic fluid volume independent of the gestational age; oligohydramnios is defined as an amniotic fluid volume less than 300 mL, and polyhydramnios is defined as an amniotic fluid volume in excess of 2,000 mL.

Clinically both oligohydramnios and polyhydramnios can be diagnosed using...
an ultrasonographic measurement of the amniotic fluid index, a summation of the maximal vertical fluid dimension visualized in the four quadrants of the uterus. The amniotic fluid index is stable at approximately 14 cm throughout the second and the third trimesters of pregnancy. An amniotic fluid index less than 5.0 cm, as in this vignette, indicates oligohydramnios, whereas an index greater than 25 cm indicates polyhydramnios.

During the latter half of gestation, fluid movement into and out of the amniotic sac uses six potential pathways (Figure).

**Figure: Amniotic fluid balance**

The entry of fluid into the amniotic sac is influenced largely by fetal urine production, to a lesser extent by fetal lung liquid synthesis, and only partly by fetal oral/nasal secretion. The exit of fluid from the amniotic sac is influenced largely by fetal swallowing and partly by fetal membrane fluid flux. The latter has two components: (1) intramembranous fluid flux which represents movement of water and solutes between amniotic fluid and fetal blood (in the placenta as well as in the umbilical cord), and (2) transmembranous fluid flux which represents movement of water and solutes between amniotic fluid and maternal blood within the wall of the uterus.

The largest contributor to amniotic fluid volume in the latter half of pregnancy is fetal urine production. Based on ultrasonographic measurements of fetal urinary bladder volume, the fetal urine production is estimated at 200 mL/kg of body weight per day. Any fetal condition that precludes the formation of urine (for example, renal agenesis or dysplasia) or prevents its release into the amniotic sac (for example, obstructive uropathy) often results in oligohydramnios. Whereas low fetal urine production and oligohydramnios are known to be associated, no such association has been shown between excess fetal urine production and polyhydramnios. The latter is most often the result of reduced amniotic fluid clearance.

The second major contributor to amniotic fluid volume in the latter half of pregnancy is fetal lung liquid synthesis. To date, the precise rate of lung liquid synthesis has not been determined in the human fetus. Based on ovine studies that mimic the human condition, the fetal lung liquid synthesis during the latter third of gestation is estimated at 100 mL/kg of body weight per day. Fetal lung liquid secretion is mediated by an active chloride transport in the pulmonary epithelium. Only approximately 50% of the fetal lung liquid is believed to enter the amniotic sac, whereas the remainder is swallowed by the fetus upon its exit via the trachea.

A minor contributor to amniotic fluid volume in the latter half of pregnancy is fetal oral/nasal secretion. Based on ovine studies, the fetal oral/nasal secretion rate during late gestation is estimated at 8.0 mL/kg of body weight per day.
Fetal swallowing represents the major route of amniotic fluid resorption. Limited human studies have shown that fetal swallowing increases steadily throughout gestation from an estimated average of 50 mL/kg of body weight per day at 18 weeks to a peak average of 155 mL/kg of body weight per day (range, 70-260 mL/kg of body weight per day) at term. Swallowing occurs primarily during episodes of fetal breathing, and it decreases to near zero just before the onset of labor and delivery. Any fetal condition that precludes swallowing (for example, anencephaly) or that impairs swallowing (for example, high gastrointestinal obstruction such as esophageal atresia) often results in polyhydramnios.

A minor contributor to amniotic fluid resorption in the latter half of pregnancy is fetal membrane fluid flux. Based on ovine studies, the intramembranous fluid flux between amniotic fluid and fetal blood is estimated at 60 mL/kg of body weight per day, whereas the transmembranous fluid flux between amniotic fluid and maternal blood is estimated at 3.0 mL/kg of body weight per day.

In this vignette, in the absence of a history of prolonged leakage of amniotic fluid, it is prudent to examine the fetus for abnormalities of renal structure and function as a cause of oligohydramnios.

References:


American Board of Pediatrics Content Specification(s):

Know how to diagnose oligohydramnios, its significance and the management of pregnancy when it is diagnosed

Know how to diagnose polyhydramnios, its significance and the management of pregnancy when it is diagnosed
A nurse in your neonatal intensive care unit comes to you with an urgent request. She has just had a routine 30-minute prenatal ultrasound study of her 26-week-gestation fetus, during which no fetal breathing movements were seen. She is scheduled to see her obstetrician on the next day for an interpretation of the ultrasound study, but she wants to know now if she could have done anything to inhibit the fetal breathing movements.

Of the following, the maternal factor MOST likely to inhibit fetal breathing movements is:

1. betamethasone
2. hyperglycemia
3. hyperoxia
4. indomethacin
5. labor

You selected 2, the correct answer is 5.

Fetal breathing movements (FBMs) are present from the 10th week of gestation. Their frequency increases with gestational age to 6% of the time by 19 weeks, 14% of the time by 26 weeks, and up to 50% of the time by the last 10 weeks of pregnancy. Some factors that lead to increased or decreased FBMs in the last 10 weeks of pregnancy are listed (Tables 1 and 2). Labor at any gestational age is the factor most likely to inhibit FBMs.

**Table 1. Some Maternal Factors That Increase Fetal Breathing Movements**

<table>
<thead>
<tr>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoventilation or breathing 2%-4% CO₂</td>
</tr>
<tr>
<td>Hyperoxia, if intrauterine growth-restricted fetus</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Glucose infusions after maternal fasting; maternal postprandial glucose rise</td>
</tr>
<tr>
<td>Smoking (faster breathing rate, but more time spent apneic)</td>
</tr>
<tr>
<td>Acute caffeine dose of 454 mg (not seen with 200 mg)</td>
</tr>
<tr>
<td>Betamethasone, terbutaline, or indomethacin</td>
</tr>
</tbody>
</table>

**Table 2. Some Maternal Factors That Decrease Fetal Breathing Movements**

<table>
<thead>
<tr>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperventilation</td>
</tr>
<tr>
<td>Hypoxemia with acidemia, but not hypoxemia alone</td>
</tr>
<tr>
<td>Labor or approaching labor</td>
</tr>
<tr>
<td>Hypothermia</td>
</tr>
<tr>
<td>Alcohol, barbiturates, methadone, or prostaglandin E₂</td>
</tr>
</tbody>
</table>
Very little fluid is exchanged during FBMs, with volumes estimated as 0.5 mL or less per breath. During periods of breathing, the respiratory rate is usually 40 to 60 breaths per minute. These breathing periods are episodic: in normal third-trimester fetuses, no FBMs are seen in 8% of the observed 30-minute intervals, the typical observation interval during an ultrasound study used to determine a biophysical profile of the fetus.

The FBMs decrease within 3 days of preterm or term birth, mediated by increasing maternal serum concentrations of prostaglandin E₂ and blocked by prostacyclin inhibitors such as indomethacin. These changes have been described using pooled data comparing the mean values from groups of patients. Attempts to use a decrease in FBMs to predict imminent onset of labor for a specific individual have been unsuccessful. During active labor, FBMs are seen less than 10% of the time.

Other maternal medications affect FBMs. Stimulants, such as terbutaline or cocaine, cause increased FBMs. Depressants, such as alcohol or magnesium sulfate, decrease FBMs. The mechanism by which betamethasone increases FBMs may involve greater uterine blood flow and oxygen delivery to the fetus.

Hyperoxia in a normal pregnancy is not associated with any change in FBMs. Hyperoxia in a pregnancy with intrauterine growth restriction causes increased FBMs. Hypoxemia with acidemia is associated with decreased FBMs, but hypoxemia alone is not.

Hyperglycemia causes increased FBMs if the mother has fasted. This includes the daily fasting between meals: the second and third hours after a normal meal during pregnancy are associated with increased FBMs. Chronic hyperglycemia without fasting, as in a diabetic mother, causes no change in FBMs.

Maternal cigarette smoking may have several different effects on FBMs. Some reports find an increase in the breathing rate, but also an increase in the number of long periods of apnea that can confound the scoring of a biophysical profile. Other reports find that smoking abolishes FBMs, and still others observe no significant change.

The most important application of FBMs is with the biophysical profile. The biophysical profile involves detection of FBMs and four other items: muscle tone, body movement, heart-rate changes (the nonstress test), and amniotic fluid volume. No single item is very predictive. The five items are combined in a biophysical profile score of 0 to 10, assigning either a 0 or 2 to each item. A score of less than 6 has been associated with increased perinatal mortality and often leads to delivery.

References:


**American Board of Pediatrics Content Specification(s):**

Know the factors affecting control of fetal breathing movements
Understand the rationale, interpretation, and shortcomings of maternal detection of the biophysical profile as a means of assessing fetal well-being.
A woman who is 35 weeks' pregnant requests a cesarean section delivery in 3 weeks. She has a history of irregular menstrual periods and is not certain of her last menstrual period. The women's obstetrician has performed a number of clinical and ultrasonographic assessments to determine the gestational age of the fetus.

Of the following, the assessment or finding that MOST accurately indicates the gestational age of this fetus is:

1. embryonic crown-rump length
2. fetal heart tones
3. fundal height
4. gestational sac diameter
5. Naegle's rule

You selected 1, the correct answer is 1.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

Knowledge of gestational age is vital for obstetric and neonatal decision-making. Precise determination of the gestational age of the pregnancy would require detection of the date of implantation of the conceptus into the uterus. Currently, no tools are available to provide such accurate information. During the initial stages of a pregnancy, minor inaccuracies (4-6 days) exist in determining the gestational age and estimated date of delivery even when a mother is confident about the dates of her last menstrual period. The inaccuracies occur because of inherent biological variation in time to fertilization of the egg and time to blastocyst implantation. Assisted reproductive techniques may define the time of fertilization but timing of implantation of the blastocyst will vary.

Ultrasoundography is an essential tool for dating pregnancies, especially when a mother has irregular menstrual periods, early pregnancy bleeding, poor recall, or has been taking oral contraceptive medications. The crown-rump length is the standard measurement of the embryo during the first trimester (Table).
The greatest length of the embryo from the outer edge of the cephalic pole to the rump determines the crown-rump length (http://www.emedicine.com/med/topic3236.htm). Although the gestational age can be projected based on the crown-rump length using tables, the gestational age in days can be estimated for embryos smaller than 25 mm by adding 42 to the crown-rump length. Ultrasonographic measurement of the crown-rump length is accurate to ±3 days when the gestation is between 7 and 10 weeks. This is the most accurate indicator of the gestational age of the fetus. The accuracy of crown-rump length decreases to approximately 5 days at a gestation of 10 to 14 weeks' and thereafter is no longer predictive.

Cardiac activity can be detected with ultrasonography beginning at about 6 weeks' gestation in the embryo that is too small to measure a crown-rump length. Fetal heart activity can be detected using Doppler technology beginning at about 12 weeks' gestation. Fetal heart tones can be auscultated with a fetoscope at approximately 20 weeks' gestation. Both measurements are accurate to ±2 weeks.

Fundal height, or uterine size, is a physical finding that increases as gestation proceeds and is accurate to ±3 weeks. The uterus is normally a pelvic organ until 12 weeks' gestation. The size of the uterus during the early weeks of gestation has been compared to the size of different fruits:

- 6 to 8 weeks' gestation: Small pear
- 8 to 10 weeks' gestation: Orange
- 10 to 12 weeks' gestation: Grapefruit

After 12 weeks' gestation, the uterus enters the abdomen where the fundus can be palpated:

- 16 weeks' gestation: Midway between symphysis pubis and umbilicus
- 20 weeks' gestation: Umbilicus

The gestational sac initially lies in the endometrium and is the first ultrasonographic sign of an intrauterine pregnancy. The gestational sac is composed of the chorionic cavity, implanting chorionic villi, and decidua tissue. No distinct structures are seen in the sac when it first presents. When the gestational sac is detectable, usually when 2 to 3 mm in size, the correlating gestational age is about 4 weeks + 1 to 3 days. There are tables that correlate gestational sac diameter and mean

<table>
<thead>
<tr>
<th>Table. Antenatal Gestational Age Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
</tr>
<tr>
<td>Last menstrual period</td>
</tr>
<tr>
<td>Uterine size-1st trimester</td>
</tr>
<tr>
<td>Fetal heart tones-auscultation</td>
</tr>
<tr>
<td><strong>Ultrasonography</strong></td>
</tr>
<tr>
<td>Gestational sac diameter</td>
</tr>
<tr>
<td>Embryonic crown-rump length</td>
</tr>
<tr>
<td>Biparietal diameter, femur length, cerebellar transverse diameter</td>
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</table>
sac diameter with gestational age in days. Accuracy of gestational sac measurements is ±5 days because the sac may not remain spherical. In addition, the yolk sac is the first structure to be ultrasonographically detected in the gestational sac (about 5 weeks' gestation) and is used to confirm an intrauterine pregnancy. On ultrasonography, the embryonic disk then appears in the gestational sac at about 5 to 6 weeks' gestation.

Naegle's rule is the most common method of dating a pregnancy and estimating the date of delivery (EDD). The rule depends on knowledge of the first date of the last menstrual period (LMP):

\[
\text{LMP [plus 1 year]} - 3 \text{ months} + 7 \text{ days} = \text{EDD}
\]

This rule is accurate to ±2 weeks and assumes a 28-day menstrual cycle, fertilization on day 14 after the first date of the LMP, and implantation of the blastocyst by 21 days. Inaccuracies occur because of irregular menstrual periods, vaginal bleeding early in pregnancy, and use of oral contraceptive medications.

References:


American Board of Pediatrics Content Specification(s):

Know the ultrasound findings and their limitations in determining gestational age
A 24-year-old woman has had insulin-dependent diabetes mellitus for 12 years. She reports an occasional need to increase her insulin dose after admitted dietary transgressions, but fears hypoglycemia even more than hyperglycemia. She has experienced two hypoglycemic events in the past year. Her physical examination findings are normal; her body mass index is 22.5 kg/m²; and her hemoglobin A1c is 7.0%. Her creatinine concentration is mildly elevated at 1.4 mg/dL (124 μmol/L) with creatinine clearance of 75 mL/min (1.25 mL/s). Her neurologic examination findings are normal, and retinal examination shows a few soft exudates. She wishes to become pregnant and to minimize the effect of her diabetes on her fetus and herself. She is being treated with a goal of achieving rigid glycemic control to lower the risk of fetal congenital anomalies and fetal macrosomia.

Of the following, strict glycemic control before and during early pregnancy in this woman is MOST associated with potential worsening of hypoglycemia and an increased maternal risk of:

1. gastroparesis
2. infertility
3. nephropathy
4. neuropathy
5. retinopathy

You selected 3, the correct answer is 5.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

Strict glycemic control is a mainstay in the management of the insulin-dependent diabetic woman. Because hyperglycemia is teratogenic, a tighter control of blood glucose concentrations in the preconceptional period and early pregnancy has been documented to reduce the risk of fetal congenital anomalies. To achieve this fetal benefit, however, the woman in this vignette risks exacerbations of hypoglycemia as well as progression of her retinopathy.

Maintenance of euglycemia is defined as keeping hemoglobin (Hb) A1c concentration within the normal range. The rates of miscarriage and fetal anomalies remain at the baseline (rates in nondiabetic pregnant women) when HbA1c concentration is no greater than 1% above normal. The recommendations of the American College of Obstetricians and Gynecologists for women with type 1 diabetes during pregnancy suggest glucose concentrations shown in the Table.
Maintaining blood glucose concentrations at euglycemic levels before or in early pregnancy has been demonstrated to reduce the risks of preterm delivery (<34 weeks' gestation) and fetal death, especially late-pregnancy stillbirth. One half of all cases of late-pregnancy stillbirth have been associated with uncontrolled hyperglycemia. The earlier that euglycemia is established, the lower is the incidence of fetal macrosomia: women whose mean self-monitored blood glucose concentration is less than or equal to 86 mg/dL (4.8 mmol/L) have one fourth the risk of fetal macrosomia than those with mean blood glucose concentrations exceeding 106 mg/dL (5.9 mmol/L). Reduction in macrosomia is associated with fewer cesarean births, less shoulder dystocia, fewer birth-injured infants, and easier control of neonatal glucose concentrations.

Among women with demonstrated retinopathy, the potential for progression of retinopathy during pregnancy is high. It varies from 10% of cases if no retinopathy were seen before pregnancy, to 21% if mild changes had been present (as in the woman in this vignette), and up to 55% if severe retinal changes preceded pregnancy. These changes are more likely if restoration of euglycemia is associated with pregnancy because the decrease in mean blood glucose concentrations is postulated to precipitate closure of narrowed, but previously patent, small retinal blood vessels. Current recommendations are that blood glucose concentrations be normalized before pregnancy and the patient be followed up by the retinologist before and during pregnancy.

Strict glycemic control also presents increased risk of hypoglycemia, especially during early pregnancy and if nausea and vomiting accompany pregnancy. Pregnancy alters glucose metabolism: after eating, transient hyperglycemia is potentiated by pregnancy-related insulin resistance; the continuous maternal and fetal requirement of glucose can result in hypoglycemia, especially at night. Nocturnal hypoglycemia may produce rebound hyperglycemia reflected in higher early morning blood glucose concentrations. In a nonpregnant woman, the risk of hypoglycemia correlates with the history and severity of hypoglycemic episodes and with the patient’s ability to detect hypoglycemia. These combined effects justify more frequent blood glucose testing and adjustments in insulin administration (both intervals and dose, and perhaps formulation of the insulin itself). Exceedingly strict control may result in lower incidence of macrosomia, but paradoxically also has been associated with greater prevalence of intrauterine growth restriction (not because of any anomaly). Of note, hypoglycemia has not been associated with fetal teratogenesis. Maintaining the glycemic balance requires management by an experienced team and a cooperative patient.

Although the diabetic complications of gastroparesis, nephropathy, and peripheral neuropathy may preexist in the pregnant woman, pregnancy itself is not an independent predictor of these diabetic complications. Among women with severe nephropathy, not suggested in this vignette, pregnancy may be associated with significant risks of fetal loss and maternal hypertension. Strict glycemic control has not been documented to reduce the incidence of preeclampsia among diabetic women. Infertility is not associated with a stricter control of diabetes.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

References:


American Board of Pediatrics Content Specification(s):

Know the components of pre-pregnancy nutrition on individuals with disease states such as type 1 diabetes

Understand the hormonal factors that affect intrauterine growth

Understand the relationship of maternal blood glucose to fetal glucose uptake and metabolism
December: Question 3

A 33-year-old pregnant woman presents to the emergency department at 21 weeks' gestation with acute hypoxemia (oxygen saturation 84%) because of an asthma exacerbation. This is the second exacerbation during this pregnancy.

Of the following, the risk factor MOST associated with asthma exacerbations during pregnancy is:

1. atopy
2. Caucasian race
3. female fetus
4. severity of asthma
5. viral infection

You selected 3, the correct answer is 1.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

Asthma is one of the most common chronic pulmonary disorders that can complicate pregnancy. Between 3% and 12% of pregnant women have asthma, and the prevalence, morbidity, and mortality appear to be increasing. Complications found in pregnant women with severe asthma may include having a low-birthweight infant, preterm delivery, cesarean delivery, preeclampsia, asthma exacerbations, and rarely, death.

Approximately 20% of women with asthma experience exacerbations. One third of these episodes lead to hospitalization (5.8% of all women with asthma). Although likely an underestimate, one third of women with asthma experience a worsening of their condition during pregnancy, whereas one third remain unchanged and one third improve. The peak time for deterioration during pregnancy clusters around 20 weeks' gestation. Approximately 18% of women with asthma experience asthma symptoms during labor. Among women with severe asthma, 46% experience symptoms during labor.

The most important risk factor for exacerbation of asthma during pregnancy is severe asthma. Exacerbation rates generally increase with the severity of maternal asthma:

- Mild asthma
  - Exacerbation rate: 12.6%
  - Hospitalization rate: 2.3%
- Moderate asthma
  - Exacerbation rate: 25.7%
  - Hospitalization rate: 6.8%
• Severe asthma
  - Exacerbation rate: 51.9%
  - Hospitalization rate: 26.9%

A severity classification for asthma during pregnancy was developed by the Working Group on Asthma and Pregnancy sponsored by the National Institutes of Health (Table).

<table>
<thead>
<tr>
<th>Classification</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild, intermittent</td>
<td>• Symptoms twice per week or less</td>
</tr>
<tr>
<td></td>
<td>• Nocturnal symptoms twice per month or less</td>
</tr>
<tr>
<td></td>
<td>• PEFR or FEV1 80% predicted or more, variability &lt;20%</td>
</tr>
<tr>
<td>Mild, persistent</td>
<td>• Symptoms more than twice per week but not daily</td>
</tr>
<tr>
<td></td>
<td>• Nocturnal symptoms more than twice per month</td>
</tr>
<tr>
<td></td>
<td>• PEFR or FEV1 80% predicted or more, variability 20%-30%</td>
</tr>
<tr>
<td>Moderate, persistent</td>
<td>• Symptoms daily</td>
</tr>
<tr>
<td></td>
<td>• Nocturnal symptoms more than once per week</td>
</tr>
<tr>
<td></td>
<td>• PEFR or FEV1 60% to 80% predicted, variability &gt;30%</td>
</tr>
<tr>
<td>Severe</td>
<td>• Continuous symptoms and frequent exacerbations</td>
</tr>
<tr>
<td></td>
<td>• Frequent nocturnal symptoms</td>
</tr>
<tr>
<td></td>
<td>• PEFR or FEV1 &lt;60% predicted, variability &gt;30%</td>
</tr>
<tr>
<td></td>
<td>• Regular oral corticosteroids</td>
</tr>
</tbody>
</table>

PEFR, peak expiratory flow rate; FEV1, forced expiratory volume in 1 minute.

Failure to comply with medical treatment, especially inhaled corticosteroids, contributes to worsening of asthma. Pregnant women with asthma who regularly comply with use of inhaled corticosteroid treatment have a 75% reduction in frequency of asthma exacerbations.

Atopy is not a risk factor for exacerbation of asthma during pregnancy. Nonatopic asthma was associated with more episodes of acute asthma symptoms than atopic asthma in a single study.

Black race is a risk factor for worsening asthma. Being African American increases the incidence of asthma-associated hospitalizations, emergency department visits, and use of rescue oral corticosteroids for asthma during pregnancy. It is speculated that absent or limited prenatal care may confound this association.

In contrast to previous literature postulating an association between female fetus and maternal asthma exacerbation, current studies do not support this relationship.

Asthma symptoms often worsen during infectious illnesses. Approximately 35% of pregnant women with asthma experience viral upper respiratory illnesses or urinary tract infections compared with 5% of pregnant women without asthma. Furthermore, pregnant women with more severe disease are more susceptible to infections and exacerbation of asthma symptoms.

References:


Murphy VE, Gibson PG, Smith R, Clifton VL. Asthma during pregnancy: mechanisms and
treatment implications. *Eur Respir J.* 2005;25:731-750


American Board of Pediatrics Content Specification(s):

Know the effect of maternal acute and chronic pulmonary disease and their management on the fetus
You are asked to join an obstetric colleague to counsel a 23-year-old woman who is planning for her first pregnancy. She weighs 320 pounds (145 kg) but is otherwise healthy.

Of the following, the outcome MORE likely to occur regarding pregnancy in this woman compared with nonobese women is:

1. fertility
2. live birth
3. preeclampsia
4. type 1 diabetes
5. vaginal birth

You selected 2, the correct answer is 3.

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The incidence of maternal obesity, body mass index (BMI) of 30 kg/m² or greater, is increasing. During the last decade, the incidence of maternal obesity has doubled from 9.4% to 18.9% and the mean BMI is 1.37 kg/m² higher. About 23% of pregnant women are obese. The epidemic of obesity has important implications for the health of women and their offspring (Table).
Hypertension and obesity are significantly correlated. During pregnancy, obese women are at greater risk for gestational hypertension (4.8% in normal weight versus 10.2% in obese women) and preeclampsia (9.7% in normal weight versus 24.2% in overweight versus 35.4% in obese women). The risk of preeclampsia doubles for each 5 to 7 kg/m² increase in pre-pregnancy BMI.

Infertility and miscarriage rates are significantly increased in obese women. These problems may be related to the higher incidence of polycystic ovary syndrome in obese women (about 50%) compared with lean women (about 30%). The rate of miscarriage is about 30% higher in obese women than in normal weight women. Further, obesity is a significant risk factor for miscarriage following the use of assisted reproduction technologies.

Antepartum still birth, or late fetal death, complicates pregnancies of obese women with increasing risk as the BMI increases. The overall stillbirth rate is also increased twofold in obese pregnant women (about 9 per 1,000 deliveries) as is the neonatal death rate (about 6 per 1,000 live births). One hypothesis for the relationship between maternal obesity and stillbirth/neonatal loss suggests that the fetus may outgrow the capacity of the placenta to supply sufficient oxygen to meet the growth and energy demands of the rapidly growing fetus. Delivery of macrosomic infants before full term may reduce the rate of late fetal and neonatal death.

Obese and morbidly obese (BMI =35 kg/m²) women experience gestational diabetes more frequently. The incidence of gestational diabetes in normal weight pregnant women is 2.3% compared with 6.3% in obese women and 9.5% in morbidly obese women. Importantly, gestational diabetes is highly predictive of the development of type 2 diabetes mellitus. Thirty percent of lean women and 70% of obese women will develop type 2 diabetes within 15 years of pregnancies complicated by gestational diabetes. Because of gestational diabetes and hypertensive disorders of pregnancy, obese women have a 1.5-fold greater risk of preterm delivery.

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<th>Hypertension</th>
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<td>- Epidural catheter and endotracheal tube placement difficulty</td>
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Table. Maternal Obesity and Related Medical Issues

Hypertension and obesity are significantly correlated. During pregnancy, obese women are at greater risk for gestational hypertension (4.8% in normal weight versus 10.2% in obese women) and preeclampsia (9.7% in normal weight versus 24.2% in overweight versus 35.4% in obese women). The risk of preeclampsia doubles for each 5 to 7 kg/m² increase in pre-pregnancy BMI.

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Obese and morbidly obese (BMI =35 kg/m²) women experience gestational diabetes more frequently. The incidence of gestational diabetes in normal weight pregnant women is 2.3% compared with 6.3% in obese women and 9.5% in morbidly obese women. Importantly, gestational diabetes is highly predictive of the development of type 2 diabetes mellitus. Thirty percent of lean women and 70% of obese women will develop type 2 diabetes within 15 years of pregnancies complicated by gestational diabetes. Because of gestational diabetes and hypertensive disorders of pregnancy, obese women have a 1.5-fold greater risk of preterm delivery.
Maternal obesity presents a number of challenges that may complicate labor and delivery, such as:

- Difficulty in monitoring the fetus and uterine contractions
- Difficulties associated with anesthesia (such as inability to place epidural catheters, endotracheal tubes, and intravenous catheters) and higher risk of aspiration during general anesthesia
- Failure to deliver vaginally because of fetal macrosomia and suboptimal uterine contractions
- Surgical risks associated with large pannus (such as infection of the incision, altered surgical approach, vertical versus low transverse incision)

Cesarean rates increase with BMI. For nulliparous women, cesarean delivery for nonobese women was 21% compared with 34% and 48% in obese and highly obese women, respectively. Postdelivery complications also occur more frequently in obese women: endometritis, hemorrhage, infections, and prolonged hospitalizations. Postpartum hemorrhage is 70% more frequent in very obese women compared with normal weight women. In addition, in women with BMI greater than 30 kg/m², wound and urinary tract infections are 2.2-fold and 1.4-fold more frequent, respectively, than in nonobese women.

The prevalence of thromboembolism increases during pregnancy and is associated with the 60% increase in venous stasis by 36 weeks of gestation. In one study, the prevalence of thromboembolism during pregnancy was 0.04% in normal weight women compared with 0.07% and 0.08% in overweight and obese women, respectively.

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References:


American Board of Pediatrics Content Specification(s):

- Know the effect of diabetes mellitus and its treatment on the fetus
- Know the effects on the fetus of maternal endocrine disorders (other than diabetes mellitus) and their management
- Know the general principles, applications, and limitations of ultrasonography, including Doppler blood flow, in assessment of fetal conditions, and well being
- Understand the implications of fetal macrosomia
- Understand the effects on the fetus of maternal metabolic disorders (other than diabetes mellitus) and their management
A 40-year-old pregnant woman presents to the hospital in preterm labor at 24 weeks' gestation. She has severe asthma and has been to the emergency department three times during this pregnancy for exacerbations of asthma. She uses inhaled corticosteroids regularly. You are discussing with the care team the physiologic changes that occur in the respiratory system during pregnancy and how asthma may predispose this woman to fetal hypoxemia.

Of the following, the characteristic MOST consistent with respiratory physiology in pregnancy is that:

1. functional residual capacity increases
2. peak expiratory flow rate is unchanged
3. residual volume increases
4. respiratory rate decreases
5. tidal volume remains unchanged

You selected 2, the correct answer is 2.

Pregnancy requires dramatic physiologic and metabolic adaptations to supply the nutrient and gas exchange demands of the growing fetus and uteroplacental mass. Although pulmonary functions such as peak expiratory flow rate, forced expiratory volume in 1 second, and forced vital capacity are not affected by pregnancy, minute ventilation and lung volumes change significantly (Figure).

Figure: Comparison of lung volumes and capacities before and during pregnancy
Pulmonary function is affected by the enlarging uterus and fetus and progesterone levels. The diaphragm may be displaced upward 4 cm and the transverse diameter of the chest may be increased 2 cm. The functional residual volume (volume of gas in the lungs at end expiration) and residual volume (volume of gas in the lungs after maximum expiration) decrease during pregnancy by 10% to 25% and 20%, respectively. Progesterone reduces airway resistance by 50%; this effect contributes to a threefold increase in expiratory reserve volume to 22% of total lung volume. Total lung volume changes little during pregnancy.

Tidal volume (TV) increases 30% to 40% and respiratory rate (RR) changes little, if any, during pregnancy. Minute ventilation (TV × RR), therefore, increases in proportion to TV and accounts for the "physiologic dyspnea" that occurs in 60% of pregnant women during exertion and in 20% at rest. Respiratory alkalosis occurs as arterial partial pressure of carbon dioxide (PaCO₂) falls to 28 to 32 torr and pH rises to 7.40 to 7.47. Bicarbonate concentration declines as renal excretion increases and hydrogen ion rises to partially compensate for respiratory alkalosis. pH is maintained in the upper normal physiologic range to reduce the negative effect of alkalosis on protein function.

Progesterone and, to a lesser degree, estrogen are responsible for the rise in minute ventilation during pregnancy. The mechanism by which these hormones increase minute ventilation is not clearly known but may include effects on body water, plasma osmolality, and concentration of cations and anions in the cerebrospinal fluid (CSF). Early in pregnancy, estrogen increases the number of progesterone receptors in the hypothalamus. Progesterone concentrations then increase during the second and third trimesters. Progesterone facilitates sodium and water retention with proportional increases in plasma and extracellular fluid volume. Estrogen impedes the exit of albumin from blood vessels, shifts fluid to the intravascular space, and lowers the osmotic threshold for vasopressin release. Fluid is subsequently retained, osmolality decreases in the plasma, and the ionic difference (strong ion difference [SID]), in concentrations of the strong cations sodium, potassium, and calcium, and the anions chloride and lactate, in CSF decrease. Lower plasma osmolality and CSF (SID) than those seen before pregnancy may stimulate the increase in minute ventilation.

The relatively lower PaCO₂ that results from increased minute ventilation during pregnancy affects the carbon dioxide (CO₂) tension gradient across the placenta, thereby facilitating CO₂ removal from the fetus. Acute increases in maternal PaCO₂ during asthma exacerbations lead to a reduced CO₂ tension gradient. Fetal hypercarbia and acidosis may cause fetal distress. The maternal oxyhemoglobin dissociation curve also is shifted leftward when partial pressure of carbon dioxide (PCO₂) decreases, causing hemoglobin to bind oxygen more tightly. Oxygen transfer to the fetus may be impeded. Oxygen delivery to the fetus may be further impaired if
maternal PaO2 and oxygen content decrease because of asthma. Because the oxyhemoglobin dissociation curve of fetal hemoglobin is steep, a small decline in fetal PaO2 is associated with a marked reduction in oxygen saturation. Oxygen delivery is potentially reduced with acute decreases in fetal oxygen saturation because the fetus has limited physiologic reserve to increase cardiac output and hemoglobin concentration.

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**References:**

Curran CA. The effects of rhinitis, asthma, and acute respiratory distress syndrome as acute or chronic pulmonary conditions during pregnancy. *J Perinat Neonat Nurs.* 2006;20:147-154


**American Board of Pediatrics Content Specification(s):**

Know the effect of maternal acute and chronic pulmonary disease and their management on the fetus

Understand organ and integrated physiology of maternal adaptation to pregnancy and know the normal changes in physiologic variables and in laboratory values

Know the role of the placenta in gas exchange and oxygenation of the fetus
A 25-year-old woman who is in her 24th week of pregnancy presents in preterm labor. Ultrasonography reveals the infant to be in the vertex presentation. Cervical examination reveals absent dilation or effacement. Contractions are infrequent after treatment with magnesium sulfate. The parents wish to be aggressive with resuscitation and stabilization if the infant is born soon. You are asked to advise about the mode of delivery, vaginal or cesarean, that is best if the infant is born during the next several days.

Of the following, the outcome MOST likely to be reduced by cesarean delivery in this infant is:

1. Asphyxia
2. Intraventricular hemorrhage
3. Mortality
4. Necrotizing enterocolitis
5. Respiratory distress syndrome

You selected 3, the correct answer is 3.

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The optimal mode of delivery in extremely preterm infants, such as the infant in the vignette, remains controversial. The physical forces that accompany uterine contractions have been proposed as an inciting mechanism for birth trauma, asphyxia, intracranial hemorrhage, ischemic brain injury, and associated long-term neurodevelopmental disabilities. Cesarean delivery has been hypothesized to obviate these complications.

A metaanalysis of six randomized trials comparing cesarean to vaginal delivery in extremely preterm infants studied a total of only 122 women; the trials were limited by difficulty in enrollment and varied by fetal presentation and presence or absence of labor. The only difference found was a higher degree of fetal acidosis measured by umbilical cord blood pH in the cesarean group. A number of observational studies have reported conflicting results about short and, to a lesser extent, long-term outcomes when comparing cesarean and vaginal delivery of extremely preterm infants.

The short- and long-term maternal risks of cesarean delivery during the early part of the third trimester are important factors when determining mode of delivery. Postoperative complications such as hemorrhage, prolonged hospitalization, infection, bladder injury, and complications during pregnancies after cesarean births (such as uterine rupture) may occur. Such complications and insufficient information about optimal mode of delivery for the preterm fetus suggest that vaginal delivery, if not contraindicated, is the preferred mode of delivery for preterm infants.

Malloy and Doshi analyzed the United States Vital Statistics Linked Birth and Infant Death Certificate file for the years 2000 to 2003 to describe the relationship between cesarean births and outcomes of extremely preterm infants and their mothers. Analytic confounders (such as errors in birthweight and gestational age, effect of the percentage of small-for-gestational-age
infants in specific birthweight categories, variation in reported age of death, complications of pregnancy and delivery, and repeat cesareans or vaginal births after cesarean) were accounted for using multivariate statistical analyses. After accounting for these confounders in the raw data (that is, trimming the data), reviewing the literature, and adjusting for key risk factors (such as small for gestational age, male, multiple birth, breech presentation, anomaly, 5-minute Apgar score less than 4, presence of medical or labor-related complications, maternal age, maternal education, and race), the following conclusions were reached about the effect of cesarean delivery on outcomes of infants born at 22 to 31 weeks' gestation compared with vaginal delivery:

- Cesarean delivery reduces neonatal mortality for infants born at 22 to 25 weeks' gestation, as in the infant in the vignette. There was no difference in neonatal mortality at 26 to 31 weeks' gestation.
- Cesarean delivery reduces neonatal mortality for infants born at 22 to 27 weeks' gestation in the presence of risk factors (such as small for gestational age, male, multiple birth, breech presentation, anomaly, 5-minute Apgar score less than 4, presence of medical or labor-related complications, maternal age, maternal education, and race). The implication is that cesarean delivery offers survival advantages in high-risk deliveries during the latter part of the second trimester.
- Cesarean delivery increases the risk of respiratory distress syndrome for infants born at 22 to 24 weeks' gestation.
- Cesarean delivery does not reduce the risk of intraventricular hemorrhage.
- Cesarean delivery may reduce the risk of having a 5-minute Apgar score less than 4.
- There is not enough information to describe a relationship between cesarean delivery and necrotizing enterocolitis.

Although the report by Malloy and Doshi provides important insights, the decision about mode of delivery must also weigh the high risk of neurologic and developmental disability among infants born at 22 to 25 weeks' gestation, maternal risks of cesarean delivery, parental preferences about aggressiveness of resuscitation and care, and complications during labor that indicate a specific mode of delivery. The findings of Malloy and Doshi also suggest that cesarean delivery of infants born after 25 weeks' gestation does not have significant outcome advantages compared with vaginal delivery. The mode of delivery after 25 weeks' gestation then becomes a function of labor and delivery complications that indicate a specific mode of delivery, parental preferences, and obstetrical judgment.

References:


Know the indications for cesarean delivery
Know the maternal and fetal/newborn complications of cesarean delivery
Know the advantages of, indications for, and complications of vaginal delivery
You are meeting with a 32-year-old primiparous woman at 14 weeks' gestation who weighs 240 pounds (108 kg) and has a body mass index of 34 kg/m². She has had no medical illnesses or complications of pregnancy.

Of the following, the MOST likely outcome for her offspring compared with the offspring of nonobese women is:

- [ ] fetal hyperinsulinemia
- [X] intrauterine growth restriction
- [ ] low adiposity during adolescence
- [ ] successful breastfeeding
- [ ] urinary tract anomaly

You selected [x], the correct answer is [1].

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The incidence of maternal obesity is increasing. During the last decade, the incidence of maternal obesity has doubled from 9.4% to 18.9%, and the mean body mass index (BMI) is 1.37 kg/m² higher. Approximately 23% of pregnant women are obese. The epidemic of obesity has important implications for the health of women and their offspring.

Fetal body size is generally larger in obese women than in those of normal weight, in large part, because of hyperinsulinemia in both mother and fetus. Obese women are more insulin resistant and have higher plasma insulin concentrations than women of normal weight. Maternal hyperinsulinemia raises the concentration of triglycerides, which allows more triglycerides (energy substrates) to be transferred to the fetus. Furthermore, maternal hyperinsulinemia increases amino acid turnover and makes amino acids more available for transplacental passage to the fetus. Amino acids are insulin secretagogues. Increased plasma concentrations of fetal energy substrates, amino acids, and insulin enable greater fetal growth in obese women than in women of normal weight.

Offspring of obese women develop fetal macrosomia independent of diabetes or maternal height. The incidence of fetal macrosomia increases as maternal BMI increases. Furthermore, birthweight has a strong correlation with maternal weight gain in nulliparous women who are not obese. Birthweight is not correlated with maternal weight gain during pregnancy among obese women. A fourfold greater number of large-for-gestational-age infants are born to overweight/obese women than to diabetic women because the incidence of overweight/obesity is much greater than diabetes in pregnant women.

Infants with macrosomia are at a two- to ninefold higher risk for obesity in adulthood than are normal weight infants. Fetuses with macrosomia, similar to low-birthweight or small-for-gestational-age infants, are at high risk to develop the metabolic syndrome (obesity, hypertension, insulin resistance, dyslipidemia) during adolescence and adulthood.
Furthermore, adiposity is increased significantly in children of obese mothers.

Breastfeeding is more difficult for women who are obese. Positioning and breast size may be challenging for the newborn infant. Suckling-induced release of prolactin, a hormone important for breast milk secretion, is impaired in some obese women.

The relationship between obesity without diabetes mellitus and congenital anomalies is unclear. Case control studies suggest a greater risk for neural tube defects, congenital heart disease, abdominal wall defects, and multiple anomalies. Urinary tract anomalies are encountered infrequently. The mechanism for the association of obesity and congenital anomalies is speculated to be similar to the fuel-mediated teratogenesis suggested for diabetes mellitus.

The ability to perform ultrasonographic fetal imaging is impeded in obese women. For women with BMI greater than the 90th percentile, the success at visualizing all fetal organ systems is about 85%. If the BMI is above the 97th percentile, the success at imaging all fetal organ systems falls to 63%. The limitations of ultrasonography in obese pregnant women emphasize the importance of maternal serum screening to detect congenital malformations.

References:


American Board of Pediatrics Content Specification(s):

Know the effect of diabetes mellitus and its treatment on the fetus

Know the effects on the fetus of maternal endocrine disorders (other than diabetes mellitus) and their management

Know the general principles, applications, and limitations of ultrasonography, including Doppler blood flow, in assessment of fetal conditions, and well being

Understand the implications of fetal macrosomia

Understand the effects on the fetus of maternal metabolic disorders (other than diabetes mellitus) and their management
A 31-year-old gravida 2, para 1 woman presents in labor at full term. Her previous pregnancy 1 year ago resulted in vaginal delivery of a 3,560 g infant in vertex presentation. During this pregnancy, maternal screening tests and fetal ultrasonography at 18 weeks' gestation revealed a normal-appearing female fetus. Rupture of membranes occurred 1 hour before admission. On arrival at the hospital, maternal vaginal and ultrasonographic examinations reveal the fetus to be in frank breech presentation with the presenting part at station 0; the cervix is effaced but undilated. Fetal heart rate is 142 beats per minute. Plans are made for cesarean delivery.

Of the following, cesarean delivery for this mother likely would REDUCE the risk of:

1. brachial plexus injury
2. maternal mortality
3. neonatal mortality
4. neurodevelopmental impairment
5. prolapse of the umbilical cord

You selected 2, the correct answer is 1.

About 3% to 4% of term pregnancies have breech presentation. The incidence of breech presentation is inversely correlated with birthweight, occurring in about 30% of low-birthweight and up to 40% of very-low-birthweight infants. Frank breech presentation, in which the fetal hips are flexed and the knees are extended, comprises about 67% of breech presentations, more so among full-term fetuses. Incomplete breech presentation, in which one or both of the fetal hips are incompletely flexed causing some part of the fetal lower extremity to precede the buttocks, comprises 25% to 35% of breech presentations and is more common among premature infants. Complete breech, with flexed fetal hips and knees, is the least common (5%) breech presentation, and complete breech often converts to incomplete breech during labor. Breech presentation is more common if fetal anomalies are present: malformations of the central nervous system exist among 1.5% to 2% of breech-presenting infants; chromosomal abnormalities are discovered among 1%; and major congenital anomalies are found in 9% of full-term and 17% of preterm breech infants.

When breech presentation is discovered at term gestation in a singleton pregnancy uncomplicated by history of a previous cesarean delivery, maternal uterine anomaly or bleeding, nuchal cord, oligohydramnios, cephalopelvic disproportion, or uteroplacental insufficiency, external cephalic version may be successful in converting to cephalic presentation and allow for vertex vaginal delivery. Nevertheless, mothers having a successful external version continue to have higher rates of operative deliveries (instrumental or cesarean delivery) than spontaneously occurring vertex deliveries.

The route of delivery for full-term, breech-presenting neonates has been evaluated in a number of studies, most of which suggest improved outcome after cesarean delivery. Vaginal breech
birth in a California study of births occurring from 1991 to 1999 showed an increased risk for neonatal mortality (odds ratio 9.2; 95% confidence intervals, 3.3-25.6) and for several morbidities including asphyxia, brachial plexus injury, and birth trauma. When pregnancy histories of women who had had a previous vaginal delivery were reviewed, as in the woman in this vignette, no difference was found in neonatal mortality, but the neonatal morbidity remained high. Brachial plexus injury was noted among 0.9% of the vaginally delivered breech infants in contrast to 0.1% of vaginally delivered cephalic infants and fewer than 0.1% of cesarean-delivered breech infants.

Maternal safety has improved remarkably over the past century regardless of the route of delivery. Although cesarean delivery poses slightly increased risk to the mother associated with surgical complications or anesthesia, it is unlikely to expose her to added mortality risk. Maternal morbidity in breech presentations is similar (1.7% to 1.8%) for elective cesarean and successful vaginal deliveries, but emergency cesarean delivery (required in 40%-50% of attempted vaginal breech labors) is associated with a higher (2.8%) morbidity rate.

Population-based studies have described associations between vaginal breech delivery and short-term morbidities such as seizures, birth trauma, and hypoxic-ischemic encephalopathy, leading to concerns about the longer-term effect of breech delivery. The International Term Breech Trial attempted to evaluate rates of death or neurodevelopmental delay among breech-presenting infants. This trial failed to demonstrate significant differences for either outcome; however, the study was powered only to find relatively large intergroup differences. Evaluation of breech-born children at 4 to 5 years likewise failed to demonstrate neurodevelopmental impairment as a function of the mode of delivery. These long-term findings are reassuring regarding a choice for vaginal breech delivery, but the findings do not change either the improved neonatal mortality (for nulliparous women) or reduced short-term neonatal morbidities associated with cesarean delivery.

Cord prolapse is a risk associated with breech delivery, but the woman in this vignette presented after membrane rupture with no signs of fetal heart irregularity and with the presenting part in a frank beech presentation at station 0, thus having avoided this risk by the time of her presentation.

For breech-presenting pregnancies at term, cesarean delivery is the recommended and preferred route of delivery according to the American College of Obstetricians and Gynecologists 2006 Consensus Statement #340. This statement allows for vaginal delivery in some circumstances, but notes that the availability of fewer obstetricians with adequate clinical experience with vaginal breech deliveries was a major factor in its recommendation for planned cesarean delivery.

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References:


American Board of Pediatrics Content Specification(s):

Know the causes of maternal and neonatal complications and the management of abnormal presentations, such as breech, shoulder dystocia, etc
Know the indications for cesarean delivery
A 20-year-old primiparous woman presents at 30 weeks' postmenstrual age with recurrent uterine contractions (four contractions every 20 minutes), premature rupture of membranes, and cervical dilation of 2 cm as seen on speculum examination. She has no signs of clinical chorioamnionitis. Her physicians wish to delay her delivery at least long enough for antenatal steroid administration.

Of the following, significant delay in progression of labor is MOST likely to follow use of a(n):

1. β-adrenergic agonist
2. calcium channel blocker
3. cyclooxygenase inhibitor
4. infusion of magnesium sulfate
5. period of absolute bed rest

You selected 4, the correct answer is 1.

Do you want to add anything to your Learning Plan?
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The mother in the vignette is in preterm labor (PTL), the definition of which varies. The symptoms of PTL most often associated with preterm delivery include uterine contraction frequency of six or more per hour, cervical dilation of 3 cm, effacement of 80%, ruptured membranes, and bleeding. The goal of tocolytic therapy for PTL is to delay delivery for 48 to 72 hours; tocolytics are unlikely to prolong pregnancy by weeks or months. There are no evidence-based guidelines for when to initiate treatment of PTL. Tocolysis is contraindicated when there is a lethal fetal anomaly or intrauterine fetal demise. Nonreassuring fetal condition, severe fetal growth restriction, severe preeclampsia, and chorioamnionitis are considered relative contraindications to tocolysis as well. None of these relative or absolute contraindications is present in the mother in the vignette.

A Cochrane review found treatment using a β-adrenergic receptor agonist to be most associated with a decrease in the number of women giving birth within 48 hours. The β2-receptor associated with smooth muscle relaxation uses the cyclic adenosine monophosphate (cAMP) signaling system. The β-adrenergic receptor agonists effect myometrial relaxation by binding with β2-adrenergic receptors and increasing intracellular adenylyl cyclase. An increase in intracellular cAMP activates protein kinase and results in the phosphorylation of intracellular proteins. The ensuing drop in intracellular free calcium interferes with myosin light-chain kinase, which diminishes myometrial contractility by inhibiting the interaction between actin and myosin.

In a meta-analysis of randomized controlled trials, calcium channel blockers did not significantly reduce the risk of birth within 48 hours of initiation of treatment. Calcium channel blockers decrease intracellular free calcium by directly blocking the influx of calcium ions through the cell membrane and inhibiting release of intracellular calcium from the sarcoplasmic reticulum. The decrease in intracellular free calcium inhibits calcium-dependent
myosin light-chain kinase phosphorylation and results in myometrial relaxation.

According to the Cochrane database, data comparing cyclooxygenase (COX) inhibitors with placebo for treatment of PTL are scant. Although the numbers are small, compared with placebo, COX inhibition showed a trend in reduction in risk of delivery within 48 hours of initiation of treatment, but more data are needed. Indomethacin is a nonspecific COX inhibitor. COX is the enzyme that converts arachidonic acid to prostaglandins, which are vital in parturition. Prostaglandins enhance the formation of myometrial gap junctions and increase intracellular calcium by raising transmembrane influx and sarcolemmal release of calcium. COX exists in two isoforms, COX1 and COX2. COX1 is constitutively expressed in gestational tissues, while COX2 is the inducible form. COX2 is the isoform that dramatically increases in the decidua and myometrium during term labor and PTL.

A Cochrane review including three trials involving a total of 190 subjects concluded that there was no evidence of a clinically important tocolytic effect for magnesium sulfate. According to the Cochrane database, treatment with magnesium sulfate did not significantly reduce the risk of birth within 48 hours. Magnesium administration results in a transient decrease in total and ionized serum calcium concentration because of parathyroid hormone suppression. The exact mechanism through which magnesium affects uterine contractility is not completely understood; it is likely that magnesium competes with calcium at the level of the plasma membrane and inhibits myosin light-chain kinase activity by competing with intracellular calcium at this site. Interference with the activity of myosin light-chain kinase reduces myometrial contractility.

Clinicians often prescribe bed rest for treatment of PTL. The Cochrane database includes no evidence that, compared with usual activity, bed rest at home or in the hospital is either beneficial or harmful in preventing preterm birth.

References:


American Board of Pediatrics Content Specification(s):

Understand the diagnosis and management of maternal/fetal blood loss such as placenta previa, placenta abruption, and vasa previa

Understand the physiologic and molecular biological characteristics of normal parturition

Know the effects of tocolytic agents used during pregnancy
An obstetrical colleague asks you to consult with a woman and her husband. She first saw the woman at 12 weeks’ gestation after two missed menstrual periods. The ultrasonographic triad at 15 weeks confirmed the gestational age and detected no fetal anomalies. They wish to consider a cesarean delivery for their first pregnancy at 39 weeks’ gestation, without onset of labor or trial of vaginal delivery. The obstetrician indicates that she has thoroughly discussed short- and long-term consequences of cesarean birth. She would like you to discuss the potential effects of elective cesarean delivery without labor on their newborn infant.

Of the following, the MOST frequent complication of elective cesarean delivery for this infant is:

1. brachial plexus injury
2. intracranial hemorrhage
3. hypoxic-ischemic encephalopathy
4. persistent pulmonary hypertension
5. sepsis

You selected 3, the correct answer is 4.

Cesarean delivery on maternal request (CDMR) is defined as the cesarean delivery of a singleton, full-term infant in the absence of medical or obstetric indications. This controversial procedure accounts for 4% to 18% of cesarean births, and is associated with shifts in attitudes of both patients and health care practitioners. Debate of this issue is considerably controversial because there is limited published information to help parents and physicians weigh the various benefits and risks on the mother and her infant.

Among maternal and fetal outcomes reviewed extensively at a conference held by the National Institutes of Health, five consequences of CDMR were supported by moderate levels of evidence: maternal length of stay (increased); maternal hemorrhage (decreased); subsequent placenta accreta or previa (increased); subsequent uterine rupture (increased); and neonatal respiratory morbidity (increased). As noted in the vignette, the obstetrician has discussed the four obstetrical consequences of CDMR. Of the complications affecting the infant, increased risk of respiratory morbidity is associated with CDMR.

Respiratory morbidity after CDMR may result from pulmonary immaturity associated with iatrogenic prematurity, or may be the result of the infant’s lack of preparedness for cardiopulmonary transition after birth. For the infant in the vignette, pregnancy dating is relatively certain. However, because the mother presents to the obstetrician in the late first trimester and the ultrasonographic dating had been done at 15 weeks’ gestation, the expected date of delivery is accurate to approximately 10 days. At “39 weeks,” she could actually be less than 38 or more than 40 weeks’ pregnant. In the early term period (37 0/7 to 38 6/7 weeks’ gestation), respiratory morbidity (transient tachypnea of the newborn, respiratory distress syndrome, persistent pulmonary hypertension) occurs more frequently than in term infants.
past 39 weeks' gestation. If gestational assessment is in error by more than 10 days, complications of late-preterm birth may affect the infant, such as thermal instability, hypoglycemia, jaundice, feeding difficulties, and the need for hospital readmission. Iatrogenic preterm birth is a major concern if CDMR becomes more prevalent. In cases with more accurate pregnancy dating, as with dating by crown-rump length at 5 to 12 weeks’ gestation (±3 days), iatrogenic prematurity and respiratory distress syndrome become less of a concern.

In spite of accurate gestational dating, full-term infants delivered by cesarean section without labor have increased risks for respiratory distress and intensive care unit admission associated with transient tachypnea ("wet lung"), persistent pulmonary hypertension, and hypoxic respiratory failure. Absence of exposure to the endogenous steroids and catecholamines released during normal labor and absence of passage through the birth canal contribute to respiratory complications after CDMR. The former stimulates transition of the pulmonary epithelium from a fluid-secreting to a fluid-absorbing surface, and the latter enhances clearance of lung fluid by pulmonary vessels and lymphatics at the time of delivery. Although respiratory morbidities are often mild and self-limited, some cases may progress to severe hypoxic respiratory failure and persistent pulmonary hypertension. Assisted ventilation, oxygen administration, and extracorporeal membrane oxygenation may be needed in a few of these infants. Persistent pulmonary hypertension occurs more commonly among infants delivered by elective cesarean than vaginal delivery regardless of gestational age. Of the options cited, this is the greatest risk for the infant in the vignette.

Brachial plexus injury is exceedingly uncommon in association with elective cesarean births, but occurs in 0.15% of vaginal deliveries. It is estimated that universal cesarean delivery would avert about 4,500 brachial plexus injuries per year, 675 of which would have been permanent.

Intracranial hemorrhages are more frequent among infants delivered vaginally and by emergency cesarean delivery than after elective cesarean delivery. Elective cesarean delivery is associated with reduced risks for neonatal encephalopathy, intrapartum death, and late stillbirth. Epidemiologic data suggest that about 5,000 elective cesarean deliveries would be needed to avert one case of hypoxic-ischemic encephalopathy.

Infants delivered through CDMR have higher risks for nonrespiratory morbidities such as hypoglycemia, hypothermia, and admission to intensive care. Lower risks for sepsis and meconium aspiration syndrome are described and fewer fetal lacerations occur in association with CDMR than with emergency cesarean delivery.

References:


Jain L, Dudell GG. Respiratory transition in infants delivered by cesarean section. Semin Perinatol. 2006;30:296-304


American Board of Pediatrics Content Specification(s):

Know the indications for cesarean delivery

Know the maternal and fetal/newborn complications of cesarean delivery

Know the advantages of, indications for, and complications of vaginal delivery
July: Question 2

A 31-year-old woman in her second pregnancy presents in preterm labor at an estimated gestational age of 34 weeks. Her first delivery was by cesarean section, and the current fetus is in breech presentation with a low-lying placenta. One week earlier, she received antenatal steroids and a short course of a β-agonist because of threatened preterm labor. On this admission, she is initially treated with a calcium channel blocker (verapamil) for tocolysis which does not successfully inhibit her preterm labor. The obstetrician discontinues the calcium channel blocker and starts a cyclooxygenase inhibitor (indomethacin) and gives an intravenous bolus infusion of magnesium sulfate. Despite treatment, the labor continues. Fetal heart rate on ultrasonography is 142 beats per minute. She receives systemic opioid analgesia (fentanyl) during preparations for cesarean delivery. General anesthesia is induced with thiopental; neuromuscular blockage effected by atracurium; and maintenance anesthesia provided using desflurane. The infant is born 18 minutes after induction of anesthesia.

Of the following, the maternal medication MOST likely to affect this newborn's delivery room care, or resuscitation if needed, is the:

1. anesthetic induction agent
2. calcium channel blocker
3. cyclooxygenase inhibitor
4. maintenance inhalational agent
5. neuromuscular blocking agent

You selected 2, the correct answer is 4.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

General anesthesia is often used when an urgent or emergency cesarean delivery is required, as was the case in this vignette. In an emergency cesarean section, general anesthesia is achieved using three agents: a rapid-acting induction agent (such as ketamine, methohexital, midazolam, propofol, or thiopental), a neuromuscular blocking agent (atracurium, pancuronium, rocuronium, or succinylcholine), and a maintenance inhalational agent (desflurane, enflurane, isoflurane, halothane, sevoflurane, or nitrous oxide). It is the maintenance inhalational agent that poses the most concern for the infant in this vignette. Maintenance inhalational anesthetics are highly lipid soluble and equilibrate rapidly across the placenta. Because equilibration and clearance are rapid, these agents are eliminated from the neonate within a few breaths after effective ventilation is established. However, if ventilation is ineffective, these compounds (except nitrous oxide) may delay the time to onset of spontaneous respiration. Infants delivered after maternal general anesthesia are more likely to have 1-minute Apgar scores lower than 7, but generally do not have acidemia at birth. When a neonate is depressed from general anesthesia as when the interval from induction to delivery is prolonged by surgical difficulties, resuscitation requires effective ventilation until spontaneous respirations are established, usually in a matter of minutes. Desflurane, as used in this vignette, may produce airway irritation, which may cause laryngospasm and affect tracheal intubation. Pharyngeal suctioning of infants exposed to desflurane also may result in laryngospasm.
The anesthetic induction agents are highly lipid-soluble compounds that cross the placenta rapidly and achieve effective plasma concentrations in the fetus. They are cleared from the maternal and fetal circulations within 10 minutes of induction and produce very little neonatal depression if the interval from induction to delivery is 10 minutes or more.

Calcium channel blockers have been used for short-term prophylaxis to facilitate obtaining maximum benefit from antepartum steroids and for prolonged tocolysis for prevention of extreme prematurity. A meta-analysis of randomized controlled trials, however, has shown that calcium channel blockers do not significantly reduce the risk of birth within 48 hours of initiation of treatment. Pharmacokinetic data demonstrate some transplacental transfer in humans. The primary fetal concern is the potential reduction in uterine and umbilical blood flow. Animal studies revealed a decrease in uterine blood flow and decreased fetal oxygen saturation with administration of calcium channel blockers; however, this has not been confirmed in humans. Doppler studies of human fetal umbilical and uteroplacental blood flow are reassuring. The fetal acid-base status in the umbilical cord at delivery has not shown any clear evidence of fetal hypoxia or acidosis, and Apgar scores are not affected. Antepartum exposure to calcium channel blockers is not likely to have any effect on neonatal resuscitation.

According to the Cochrane database, the data comparing cyclooxygenase (COX) inhibitors to placebo for treatment of preterm labor are scant. COX inhibition has shown a trend in reduction in risk of delivery within 48 hours of initiation of treatment, but more data are needed to confirm this observation. Indomethacin crosses the placenta rapidly; fetal plasma concentrations are equivalent to maternal plasma concentrations. Fetal complications of maternal indomethacin treatment have been reported primarily with prolonged use (>48 to 72 hours) in more mature fetuses (>32 weeks' gestation). Longer periods of treatment have been associated with reversible renal failure, oligohydramnios, cerebral and splanchic vasoconstriction, and constriction of the ductus arteriosus. Oliguria is the result of reduced fetal urine output from enhanced action of vasopressin with consequent reduction in renal blood flow mediated by indomethacin. Short-term tocolytic treatment with indomethacin generally has no effect on resuscitation at birth. The resuscitation of a neonate who was exposed to a prolonged course of indomethacin as a fetus, however, may be affected; ductal constriction may lead to pulmonary hypertension making it very difficult to oxygenate the neonate in the delivery room. Ductal constriction in the presence of ductal-dependent pulmonary blood flow (congenital heart disease) will also significantly affect the newborn resuscitation.

The nondepolarizing neuromuscular blocking agents (such as rocuronium, pancuronium, atracurium) cross the placenta poorly, achieving fetal plasma concentrations that are insufficient to have a clinical effect on the neonate. It is rarely necessary to reverse the neuromuscular blockade with neostigmine and atropine.

Of the other medications used in this vignette to prolong the pregnancy, magnesium sulfate also has the potential to affect the infant at the time of delivery. Magnesium freely crosses the placenta; fetal plasma concentrations approximate maternal plasma concentrations. Maternal treatment causes a clinically insignificant decrease in baseline fetal heart rate and fetal heart rate variability. Neonates delivered by women who have received magnesium sulfate may exhibit a number of signs of neuromuscular depression, including lethargy, poor feeding, decreased bowel motility, feeding intolerance, and delayed passage of meconium. Severely affected neonates are often hypotonic and present with hypoventilation or apnea. Cardiovascular effects include hypotension, electrocardiographic changes (delayed intraventricular conduction, prolonged QT intervals, atrioventricular block), and asystole when serum magnesium concentrations exceed 17 mg/dL (7 mmol/L). Magnesium-induced bradycardia or hemodynamic instability is responsive to assisted ventilation. Respiratory depression caused by fetal hypermagnesemia may influence the course of neonatal resuscitation significantly. The affected infant can be expected to respond well to assisted ventilation, with rapid improvement in heart rate and color. However, muscle tone, respiratory effort, and reflex irritability typically do not improve. Recovery, which occurs only with elimination of magnesium in the urine, may require several hours and occasionally even a few days. The key to management in the interval is assisted ventilation.

β-adrenergic agents readily cross the placenta and achieve pharmacologically effective plasma concentrations in the fetus. Short-term exposure may produce fetal tachycardia or
Transient neonatal hypoglycemia; fetal acid/base status and neonatal well-being are not compromised by these agents. Long-term tocolytic therapy with these agents has been associated with hypertrophic cardiomyopathy and fetal hyperglycemia/hyperinsulinemia followed by neonatal hypoglycemia. These drugs generally have no effect on neonatal resuscitation.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

References:

Benitz WE, Druzin ML. Drugs that affect neonatal resuscitation. NeoReviews, 2005;6;e189-e195


American Board of Pediatrics Content Specification(s):

Know the effects of tocolytic agents used during pregnancy

Differentiate asphyxia from other causes of depression at birth, including drug effects and hypovolemia

Understand the proper approach to airway management in the delivery room

Identify the potential complications of airway management in the delivery room and know their management
August: Question 8

A 51-year-old woman is interested in becoming pregnant. While taking her history, you discover that she has been pregnant five times. Three of her children were born at term and triplets were born at 32 weeks’ gestation. During her last pregnancy, she had a spontaneous abortion at 10 weeks’ gestation.

Of the following, the MOST accurate shorthand designation of the woman’s pregnancy history is:

1. gravida 4, para 5
2. gravida 4, para 6
3. gravida 5, para 4
4. gravida 5, para 6
5. gravida 7, para 6

You selected 1, the correct answer is 3.

Do you want to add anything to your Learning Plan?
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The use of shorthand designations for diagnoses, laboratories, and other medical information is common in medicine, including obstetrics and neonatology. Gravida and parity are frequently abbreviated as Gx Px, with definitions driven by local traditions and documentation forms. Use of variably defined terms can lead to confusion and inaccurate communication.

**Gravida** is defined as the number of pregnancies experienced by a woman, regardless of the outcome. In this case, the Gravida is five because she has had five pregnancies. The Gravida is not four; the spontaneous abortion at 10 weeks’ gestation is counted as a pregnancy. There is usually little confusion about the number of pregnancies, or Gravida, of women unless early spontaneous losses are undetected.

**Parity** is defined by the number of pregnancies reaching 20 weeks’ gestation or greater. The woman in this vignette had four pregnancies of more than 20 weeks’ gestation. Confusion occurs with the term parity because it is often used to describe the number of infants born after 20 weeks’ gestation. If used to depict number of infants born after 20 weeks’ gestation, the parity would be six (three term infants and three triplets). This is incorrect; parity is determined by the number of pregnancies of 20 weeks or longer, not by the number of infants born after 20 weeks’ gestation.

A shorthand designation used frequently, although inconsistently, is to have parity depict number of infants born, in sequence, after 37 0/7 weeks’ gestation (ie, at term), between 20 0/7 and 36 6/7 weeks’ gestation (ie, preterm), and before 20 0/7 weeks’ gestation (ie, spontaneous or elective abortions), and the number of living children. In this vignette, the woman’s pregnancy history would be G5 P3116. These definitions of term and preterm are inconsistent with internationally accepted definitions. Compounding the confusion in the use of these terms is the alternative definition of the last digit; the term is sometimes used to designate number of live births rather than living children. It is important to realize that these shorthand
descriptors do not accurately communicate live births versus living children and number or combinations of multiple birth pregnancies.

Another point of confusion when using shorthand to communicate maternal pregnancy history is the use of the term GxPxxxx before and after a birth. In this vignette, before the woman's miscarriage, her pregnancy history is indicated as G5 P3106. Following the miscarriage, the history is described at G5 P3116.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

References:


American Board of Pediatrics Content Specification(s):

Know the definitions used in public health issues, services and delivery
At 32 weeks’ gestation, a 25-year-old primigravida reports decreased fetal movement. Her pregnancy has been complicated by gestational diabetes. Three days ago, she was hospitalized for threatened preterm labor, and treated with betamethasone. She has been keeping a kick count chart, and during her evening assessment she counted only eight movements in 60 minutes. That afternoon, she had taken her usual 1-mile walk, but did not eat dinner before counting kicks.

Of the following, decreased fetal movement is MOST associated with:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>1</td>
<td>a large-for-gestational age fetus</td>
</tr>
<tr>
<td>2</td>
<td>a missed meal</td>
</tr>
<tr>
<td>3</td>
<td>impending labor</td>
</tr>
<tr>
<td>4</td>
<td>low-impact maternal exercise</td>
</tr>
<tr>
<td>5</td>
<td>maternal receipt of betamethasone</td>
</tr>
</tbody>
</table>

You selected 2, the correct answer is 5.

Do you want to add anything to your Learning Plan?
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The goal of antepartum fetal surveillance is to identify the compromised fetus, and thereby reduce the risk of stillbirth, neonatal morbidity, and mortality. Fetal hypoxemia and acidosis alter the patterns and frequency of biophysical activities. Initially, asphyxia causes loss of acute variables such as heart rate reactivity, breathing, and movement. With chronic compromise and poor fetal renal perfusion, amniotic fluid production diminishes.

Fetal well-being may be assessed using maternal perception of movement, cardiotocography (the monitoring of fetal heart rate and uterine contractions), and real-time ultrasonography. However, factors such as prematurity, fetal sleep-state, central nervous system abnormalities, and maternal medications can alter fetal biophysical measurements. Moreover, antepartum testing precisely identifies neither the degree nor the duration of fetal compromise, and little evidence exists to support the premise that the risk of fetal death can be reduced by such surveillance. Therefore, the indications for antepartum testing are not well defined, but testing is often included for maternal and pregnancy-related conditions in which the risk of stillbirth is increased, such as type 1 diabetes mellitus, hypertensive disorders, systemic lupus erythematosus, intrauterine growth restriction, isoimmunization, multiple gestation, oligohydramnios, and post-term pregnancy.

The mother in the vignette had been monitoring fetal movement by keeping a kick count chart. Requiring only maternal compliance, perceived fetal movement is the simplest and least costly technique for monitoring fetal well-being in the second half of pregnancy. Maternal perception of fetal motion has been correlated with movements confirmed with ultrasonography as early as 28 weeks’ gestation. Yet, the value of fetal movement monitoring to reduce stillbirth is unclear. Indeed, documented cessation of activity warns of impending fetal death, and in some
cases precedes demise by several days. Because reduced fetal activity more often implies chronic rather than acute fetal distress, kick counting may be a useful adjunctive test for fetal well-being in high-risk pregnancies. Because half of all stillbirths occur without established risk, monitoring perceived fetal movement may be useful in low-risk pregnancies as well.

Although many methods for monitoring fetal kick counts have been described, neither the optimal number of movements nor the duration for counting them has been established. One method is the daily "count to 10" technique, in which patients count how many minutes it takes to feel 10 distinct movements. A"report card" for the fetus is generated by assigning a rating of A, B, C, D, or F, where A=0 to 15 minutes, B=16 to 30 minutes, C=31 to 45 minutes, D=46 to 60 minutes, and F=more than 60 minutes. Further evaluation, such as a nonstress test, is indicated when an F rating is assigned.

Fetal behavior may be affected by medications administered to the pregnant woman. A transient change in fetal activity has been associated with the corticosteroids betamethasone and dexamethasone. Beginning on the second day and lasting up to 4 days after betamethasone administration, fetal heart rate and body and breathing movements have been observed to reduce by 20%, 49%, and 85%, respectively. Dexamethasone has been associated with a decrease in fetal breathing, but not fetal whole body movement. Neither corticosteroid has been shown to affect fetal heart rate variability or accelerations. Similarly, sedating drugs such as alcohol, barbiturates, benzodiazepines, and narcotics cross the placenta and alter fetal behavior, with fetal breathing and heart rate reactivity affected more so than fetal movement.

Because fetal kick counts rely on maternal perception, compliance and maternal concentration on fetal activity are necessary. The woman should lie on her left side for the assessment and counting can be done at any time of the day, but the evenings may be most convenient. Fetal limb and body movements, breathing, and heart rate are not affected by maternal glucose concentrations as low as 45 mg/dL (2.5 mmol/L), therefore a meal or juice intake before monitoring fetal movement is not necessary. Similarly, low-impact maternal exercise (such as 20 minutes of aerobic dance) has been shown to transiently decrease fetal breathing but not limb movement or kick response. In contrast, heavy maternal exercise (increase in maternal heart rate >90%) may result in decreased fetal motion. Fetal bradycardia and reduced variability, and cessation of body and breathing movements lasting for 20 minutes have been associated with such maternal cardiac stress. Also, movement patterns change with advancing gestational age. The fetal heart rate slows, but exhibits increased beat-to-beat variability, and motor movements are reduced but more vigorous. However, fetal activity does not appreciably decrease during the week before delivery, dispelling a common belief that decreased fetal movement predicts impending labor.

Most fetal growth abnormalities are not detected by perceived fetal movement patterns. When evaluated with ultrasonography, growth-restricted fetuses exhibit lower activity rates than appropriately grown fetuses, but these diminished rates of movement are only consistently perceived by the mother when fetal weight is lower than the 5th percentile for gestational age. Large-for-gestational age fetuses have normal activity patterns, with the exception of the severely hydropic fetus. Similarly, as few fetal conditions affect movement, kick counts are not helpful in predicting outcomes in the presence of fetal malformations. Anencephaly has been associated with excess fetal activity, while other abnormalities of the central nervous system, muscular dysfunction, and skeletal abnormalities may result in diminished movement patterns.

References:


Understand the rationale, interpretation, and shortcomings of maternal detection of fetal movement as a means of assessing fetal well-being
A 28-year-old pregnant woman had her first ultrasonographic scan at 8 weeks’ gestation, confirming a viable fetus. One week earlier, she had relaxed in a hot tub for 30 minutes after a day of skiing. She is worried about the potential effects of high temperatures on her child.

Of the following, the anomaly MOST closely associated with maternal hyperthermia is:

1. biliary atresia
2. cystic adenomatoid malformation
3. encephalocele
4. hydronephrosis
5. renal agenesis

You selected 3, the correct answer is 3.

Do you want to add anything to your Learning Plan?
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Hyperthermia is an elevated body temperature approximately 2.0°C to 2.5°C (3.6°F-4.5°F) above the normal core temperature. Hyperthermia during pregnancy can be attributed to a febrile illness, hot/humid environments, and extreme exercise (particularly in hot/humid conditions). Sauna use or hot tub exposures are additional sources of maternal hyperthermia. The teratogenic effect of hyperthermia depends on the extent, duration, and timing of the heightened temperature. Higher temperatures or longer durations of hyperthermia are more likely to cause abortions, while exposure at critical stages of development may lead to abnormalities of embryogenesis. If maternal hyperthermia is associated with a febrile illness, it is often difficult to separate the confounding effects of the illness and the therapies from the hyperthermia. In a recent database of the Hungarian Case-Control Surveillance of Congenital Abnormalities, high gestational fever was identified in 38 (21%) of 181 infants with multiple congenital abnormalities.

Hyperthermic exposure between 4 and 14 weeks’ gestation is most likely to cause central nervous system defects in humans, including encephalocele, spina bifida, anencephaly, and hydrocephalus. The pathogenesis of hyperthermia-induced neural fetal injury is attributable to cell death, a delay in neuroblast proliferation, and/or vascular disruption. Because the infant in this vignette was exposed to maternal hyperthermia during the first trimester of gestation, he or she is at risk of having an encephalocele. Maternal hyperthermia does not increase this infant’s risk of developing biliary atresia, cystic adenomatoid malformation, hydronephrosis, or renal agenesis.

In addition to having a neurologic impact on the fetus, heat exposure between 4 and 7 weeks’ gestation is associated with facial defects, including midfacial hypoplasia, cleft lip, cleft palate, micrognathia, microphthalmia, and external ear anomalies. An association of maternal hyperthermia with fetal development of hypospadias, cardiac defects, and gastrointestinal abnormalities has also been observed. Heat-induced vascular disruption has been linked to the pathogenesis of Moebius syndrome, oromandibular-limb hypogenesis syndrome, and arthrogryposis. Adverse effects of maternal febrile illnesses during the second trimester have also been reported. During this period, it is postulated that hyperthermia can trigger...
hemorrhages in fetal structures, leading to vascular disruption.

While the type of defect is determined by the developmental stage at the time of exposure, the severity and incidence of defects depend mostly on the dose. Studies have shown that first-trimester fetuses exposed to a maternal fever of 38.9°C (102°F) or above for at least 24 hours have a higher rate of major malformations (15.8% study group versus 4.5% control group) including anencephaly, transposition of the great vessels, cleft uvula, short palpebral fissures, and preauricular pit or tag.

Because studies have found that the subjective feeling of being overheated may not be enough to protect all women from teratogenic heat exposure in saunas and hot tubs, limited or no exposure is recommended to pregnant women. Specifically, pregnant women should not be exposed to a hot tub set at 40°C (104°F) for more than 10 minutes or a sauna set above 90°C (194°F) for more than 15 minutes. Countries such as Finland, with high sauna-bathing rates, do not have an increased rate of sauna-induced congenital birth defects when these limits are respected.

References:


American Board of Pediatrics Content Specification(s):

Know the effects on the fetus on maternal hyperthermia
January

ASSESSMENT PROGRESS: Total Questions: 10  Questions Answered: 4  Correct Answers: 2

Question 4

At 28 weeks' gestation, intrauterine death of a single fetus is diagnosed in a mother carrying twins. Ultrasonography the previous day had demonstrated appropriately grown and viable fetuses. A single placenta was visualized with two distinct amniotic sacs. You are asked to meet the family and discuss the possible outcomes for the surviving fetus.

Of the following, the MOST accurate statement regarding the surviving fetus of this pregnancy is that:

- A. fetal blood sampling is likely to demonstrate anemia
- B. fetal coagulation study findings are likely to be abnormal
- C. imminent delivery will reduce neurologic morbidity
- D. mortality risk is unchanged by the death of the co-twin
- E. risk for cerebral palsy is unaffected by chorionicity

Incorrect:

Correct Answer: A

Fetal death of one twin increases the risk of mortality and morbidity for the surviving twin. First trimester intrauterine death of a single fetus is common, with a “vanishing twin” reported in one in five twin gestations. Second or third trimester intrauterine death of one fetus occurs in up to 5% of twin gestations overall, and in up to 25% of twin gestations with monochorionic placentae, especially if it is a monoamniotic gestation as well. While a “vanishing twin” has little established effect on the prognosis for the surviving fetus, intrauterine death of one fetus after the first trimester has implications for mortality and morbidity. Furthermore, the outcome of twin gestations complicated by single intrauterine death is poorer when placentation is monochorionic rather than dichorionic.

Following intrauterine death of one fetus, the surviving fetus of a monochorionic gestation has an estimated risk of death in utero or in the immediate neonatal period as high as 38%. In addition, significant morbidities have been reported in nearly 25% of survivors, including multicyclic encephalomalacia, porencephaly, hydranencephaly, renal cortical necrosis, small bowel atresia, and limb defects. The risk of serious cerebral morbidity in survivors of monochorionic twin gestations experiencing single fetus death, usually manifesting as cerebral palsy, is estimated at 20% and perhaps as high as...
50%. In contrast, cerebral palsy occurs in 3% to 7% of cases involving twins of unlike sex.

Gestational age at intrauterine death and the interval to delivery affect the outcome of the surviving twin. With a first trimester loss, the outcome is almost always favorable, whereas death in the second and third trimesters yields unfavorable results in up to 60% of cases. Early second trimester intrauterine death that does not result in preterm delivery or subsequent death of the other fetus results in lower morbidity than when the death occurs later in gestation and the interval to delivery is shorter.

Two theories have been advanced to explain the complications experienced by the surviving twin after intrauterine death in a monochorionic gestation. The *embolization theory* states that passage of thromboplastic material from the dead to the healthy twin via placental anastamoses results in disseminated intravascular coagulation in the surviving fetus. Postmortem findings of infarction and necrosis in the brain and kidneys have supported this hypothesis. However, following intrauterine death, fetal blood sampling in the surviving fetus has demonstrated normal coagulation profiles.

The *hemodynamic imbalance theory*, a more recent and convincing hypothesis, states that vascular placental anastamoses allow transfer of blood from the surviving twin to the dead twin. Exsanguination may occur just before or at the time of death of the co-twin, when its blood pressure and vascular resistance drop dramatically. For the donor twin, the result is a period of hypoperfusion, hypotension, and acute fetal anemia, which may lead to death or the development of ischemic lesions, particularly periventricular leukomalacia. Fetal blood samples taken immediately before death or within 24 hours of death demonstrating profound anemia in the surviving twin support this theory. This phenomenon implies that the number and size of vascular placental anastamoses (the large shunt between the two circulations) increases the risk for poor outcome. However, insult to the surviving twin in monochorionic gestations without evidence of twin-twin transfusion syndrome has not been shown to be reduced.

Management of the monochorionic twin pregnancy after intrauterine death of one fetus is complicated. Subsequent obstetrical intervention may not influence fetal outcome. Imminent delivery adds the risks of prematurity in the surviving twin, and may not protect from neurologic morbidity. Infusion of blood or fluids to reduce hypovolemia in the surviving twin might reduce complications, but only if intervening during that critical time surrounding the death of the co-twin. However, if the risk of intrauterine death of one fetus of a monochorionic pair is high, interruption of the vascular connections between the two circulations may be an option. This is supported by more favorable outcomes in twin survivors after laser ablation of communicating vessels in the face of twin-twin transfusion syndrome.

**References:**


**American Board of Pediatrics Content Specification(s):**

01_Maternal_Fetal: Know the types of multiple gestation and the effects on the mother of multiple gestation pregnancy

01_Maternal_Fetal: Know the potential fetal complications of multiple gestation such as cord problems, twin-twin transfusion, "stuck twin," conjoined twins, etc

01_Maternal_Fetal: Know the implications and treatment options for the surviving fetus when its twin dies in utero
February

Question 10

Placenta tion in monozygotic twins is determined by the day after fertilization when the zygote splits.

Of the following, if the zygote splits 2 days after fertilization, the MOST likely complication for the fetuses is:

- A. cord entanglement
- B. discordant growth
- C. thoraco-omphalopagus conjoining
- D. twin reverse arterial perfusion sequence
- E. twin-twin transfusion syndrome

**Incorrect:**

Correct Answer: B

Monozygotic twins develop from a single fertilized ovum that splits. Depending on the timing of this division, monozygotic twins may have monochorionic or dichorionic placentation. If division occurs within 2 to 3 days after fertilization, the placentas will be dichorionic and diamniotic (DiDi), as in the vignette (Figure 1).

**Figure 1:** Dichorionic, diamniotic twins (DiDi)
Of the choices listed, discordant growth is the most common complication associated with DiDi twin gestation. Discordant fetal growth in dichorionic twins occurs for several reasons: different genetic potential of each fetus, crowding in utero, unequal sharing of placental mass, placental insufficiency, and differences in placental parenchymal lesions, such as chronic villitis or massive perivillous fibrin deposition. Approximately one third of monozygotic twins are DiDi.

If separation of the fertilized ovum occurs 3 to 8 days after fertilization, placentation will be monochorionic and diamniotic (MoDi); approximately two thirds of monozygotic twins are MoDi (Figure 2).

**Figure 2: Monochorionic, diamniotic twins (MoDi)**
All monochorionic twins have interfetal blood vessel connections in their placenta; because the twins in this vignette would have dichorionic placentas, they would not be at risk for the twin-twin transfusion syndrome (TTTS). The vascular anastomoses associated with TTTS can be superficial, with a very low resistance (arterial-arterial or venous-venous anastomoses) or deep, with high resistance (arterial-venous anastomoses). These deep anastomoses consist of a common cotyledon, with the artery of one fetus and the vein of the other joined by a capillary system within the villi beneath the chorionic plate (Figure 3).

Figure 3: Diagram of the anastomoses in a monochorionic, diamniotic placenta depicting risk for twin-twin transfusion syndrome. (From Faye-Petersen and Crombleholme [2008].)

In the donor twin, reduced vascular volume results in vasoconstriction, oliguria, oligohydramnios, reduced growth rate, end organ damage, and neurologic morbidity, and carries a high risk of mortality. The recipient twin develops hypervolemia, polycythemia, polyuria, polyhydramnios, hyperviscosity, cardiomegaly, hypoperfusion, ischemic lesions, and hydrops. Without intervention, mortality rates for both twins range from 80% to 100% when TTTS is diagnosed before 24 weeks’ gestation.

If the egg divides 8 to 13 days after fertilization, the twins will be monochorionic and monoamniotic (MoMo); fewer than 4% of monozygotic twins are MoMo (Figure 4).

Figure 4: Monochorionic, monoamniotic twins (MoMo)

Cord entanglement only occurs in MoMo twinning, as the fetuses share the same sac. In the twin reversed arterial perfusion (TRAP) sequence, a normal fetus maintains perfusion in an
acardiac fetus through arterial-arterial and venous-venous anastamoses such that the circulation of the acardiac fetus is reversed. TRAP is most often observed in the presence of monochorionic, monoamniotic placentation. The following three criteria are required to diagnose the TRAP sequence: a monochorionic placenta, reversed perfusion through arterial-arterial anastamoses in the umbilical vessels, and discordant development of the acardiac twin (including partial or complete acardia). In the normal twin in TRAP, maintenance of blood flow to the acardiac fetus often is complicated by high-output cardiac failure, hydrops, and, if untreated, death.

Conjoined twins result from division of the zygote 13 to 16 days after fertilization; the most common type is thoraco-omphalopagus (28%). Conjoined twins are classified by the site of their most prominent union, which is ventral in 87% of cases and dorsal in 13% of cases.

References:


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**American Board of Pediatrics Content Specification(s):**

01_Maternal_Fetal: Know the types of multiple gestation and the effects on the mother of multiple gestation pregnancy
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Question 5

A 32-year-old woman presents with premature rupture of membranes at 23 weeks’ gestation. This is her first pregnancy, and no previous complications have been identified. She is not in labor. Her husband asks you about the odds of impending delivery.

Of the following, the odds of delivery 4 or more weeks after premature rupture of membranes in the case in the vignette are CLOSEST to:

- A. 0%
- B. 20%
- C. 40%
- D. 60%
- E. 80%

Incorrect:
Correct Answer: B

The odds of delivery with a latency of 4 or more weeks for mothers with preterm premature rupture of membranes (PPROM) at extremely low gestations, as in the case in this vignette, are about 20%. Latency, or the duration of time between membrane rupture and delivery, is generally inversely proportional to gestational age. At term, latency after premature rupture of membranes is less than 28 hours in 95% of cases. Before 34 weeks’ gestation, PPROM is associated with a latency of 1 week or less in 93% of women. In a subset of women with PPROM before 34 weeks’ gestation who are treated conservatively with the intent to extend the pregnancy, latency is 1 week or less in just over half the cases. Women with PPROM at 23 to 25 weeks’ gestation have a 60% to 70% chance of delivery within 1 week; however, 20% of women treated conservatively will deliver after a latency of 4 or more weeks.

Preterm premature rupture of membranes occurs in about 10% of pregnancies and in about 0.7% of pregnancies during midtrimester. Rupture of membranes may occur spontaneously, especially in women with the following risk factors:

- low socioeconomic status
- lean body mass (body mass index <19.8 kg/m²)
- history of tobacco use
March

- lung disease
- previous preterm labor
- previous cervical conization
- cervical cerclage
- 2nd and 3rd trimester bleeding
- uterine overdistention from polyhydramnios or multiple gestation

These risk factors are similar to those associated with preterm labor. Approximately 30% of preterm births are associated with PPROM. Membrane rupture may also follow invasive procedures such as amniocentesis (1%-2% of procedures) and other diagnostic studies. If membranes rupture after diagnostic procedures that produce small breaks, the leak often reseals. In such cases, complications of PPROM are infrequent. If procedures that cause larger rents in the membranes (such as fetoscopy, umbilical blood sampling, percutaneous fetal surgical procedures) are performed, the risk of significant leakage is as much as 10-fold higher. Complications, such as infection, umbilical cord compression, placental abruption, neonatal sepsis, preterm labor and delivery, pulmonary hypoplasia, and fetal compression, also occur more frequently when a large disruption of fetal membranes follows an invasive uterine procedure.

When membranes rupture before 23 weeks’ gestation, the risk of fetal and neonatal death and complications is high. Approximately 20% of such infants survive, but nearly all suffer from complications of extreme prematurity. The risk of lethal pulmonary hypoplasia is approximately 50% with PPROM before 19 weeks’ gestation and 10% at 25 weeks’ gestation. The duration of severe oligohydramnios compounds the odds of developing lethal pulmonary hypoplasia; if PPROM occurs before 25 weeks’ gestation and severe oligohydramnios persists for more than 14 days, the incidence of lethal pulmonary hypoplasia is nearly 80%. Limb anomalies and other clinical features of fetal compression are frequent as is pulmonary hypertension and hypoxemic respiratory failure; air leaks often complicate the use of positive pressure ventilation in such infants.

The degree and pathologic findings of pulmonary hypoplasia after PPROM that occurs before 23 to 25 weeks’ gestation is directly related to the gestational age when membranes rupture, not when delivery occurs. There appears to be an arrest or slowing of the development of lung architecture and vasculature when severe oligohydramnios and fetal compression occur. At midtrimester, the lung is normally in the canalicular stage of development when saccular development and complexity accelerate, accompanied by capillarization of lung saccules. With arrest of alveolarization and lung vascularization, the lung architecture is simplified. This abnormality is characterized by low lung weight, low lung-to-body weight ratio of DNA, and decreased radial alveolar counts. Lung elastic tissue development is also severely impaired. With insufficient elastic recoil and a limited supply of surfactant, the lungs of extremely preterm infants with pulmonary hypoplasia are easily overdistended and difficult to deflate. After birth, these morphologic and functional changes are reflected clinically by hypoxemic respiratory failure, pulmonary hypertension, and air leaks.

References:


American Board of Pediatrics Content Specification(s):
01_Maternal_Fetal: Know the causes, complications, and management of preterm premature rupture of membranes
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ASSESSMENT PROGRESS: Total Questions: 10  Questions Answered: 7  Correct Answers: 0

Question 6

A 25-year-old woman at 37 weeks’ gestation presents with leakage of clear vaginal fluid. This is her first pregnancy and no complications have been identified. Fetal ultrasonography shows the infant to be in vertex presentation. The woman is not in labor and feels well.

Of the following, the intervention MOST indicated for this mother-fetus dyad is:

☐ A. cesarean delivery
☐ B. corticosteroids
☒ C. digital cervical examination
☐ D. oxytocin induction
☐ E. tocolysis and antibiotics

Incorrect:

Correct Answer: D

Evaluation
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Rupture of membranes before the onset of labor is referred to as premature rupture of membranes (PROM). Preterm premature rupture of membranes (PPROM) refers to rupture of membranes before onset of labor in pregnancies of less than 37 weeks of gestation.

Preterm premature rupture of membranes occurs in about 10% of pregnancies and in about 0.7% of pregnancies during midtrimester. Rupture of membranes may occur spontaneously, especially in women with the following risk factors:

- low socioeconomic status
- lean maternal body mass (body mass index <19.8 kg/m²)
- prior cervical conization
- history of tobacco use
- cervical cerclage
- second- and third-trimester bleeding
- lung disease
- previous preterm labor
- uterine overdistention (polyhydramnios or multiple gestation)
These risk factors are similar to those associated with preterm labor. Approximately 30% of preterm births are associated with PPROM.

Membrane rupture also may follow invasive procedures such as amniocentesis (1%-2% of procedures) and other diagnostic studies. If membranes rupture after diagnostic procedures that produce small breaks, the leak often reseals. In such cases, complications of PPROM are infrequent. If procedures that cause larger rents in the membranes (such as fetoscopy, umbilical blood sampling, percutaneous fetal surgical procedures) are performed, the risk of significant leakage is as much as 10-fold higher. Complications, such as infection, cord compression, placental abruption, neonatal sepsis, preterm labor and delivery, pulmonary hypoplasia, and fetal compression, also occur more frequently when a large disruption of fetal membranes follows an invasive uterine procedure.

Management of PROM is predicated on the relative risks to mother and fetus of immediate or induced delivery compared with waiting until delivery after the spontaneous onset of labor. Gestational age at the time of membrane rupture, duration of membrane rupture, severity of oligohydramnios, and pregnancy complications (such as vaginal bleeding, chorioamnionitis, abnormal fetal position, and fetal distress) influence the timing of delivery.

Management of PROM at or after 37 weeks’ gestation, as in the case in the vignette, is to effect a prompt, or expeditious, delivery. If such cases are managed expectantly, 95% of pregnant women will deliver within 28 hours. Induction of labor with oxytocin, barring indications for cesarean delivery, is usually recommended. Although concerns have been raised about the risk of neonatal and maternal infection and higher risk of cesarean delivery after oxytocin induction, these fears have not borne out to be true. One large study compared oxytocin induction for term PROM with expectant management, and found that the duration of membrane rupture (17 hours vs 33 hours), incidence of chorioamnionitis (4.0% versus 8.6%), and postpartum fever (1.9% vs 3.6%) were significantly reduced without increasing the rates of cesareans or neonatal infections.

To reduce the risk of infection in cases of PROM, digital vaginal examinations are discouraged until an active phase of labor is established. In the case in the vignette, digital vaginal examination is of secondary importance to delivery of the infant.

Pregnancies at 34 to 36 weeks’ gestation that are complicated by PPROM are delivered expeditiously, similar to pregnancies at term with PROM. Compared with expectant management, prompt delivery of late preterm infants reduces the latency until delivery, risk of chorioamnionitis, and incidence of metabolic acidosis. For pregnancies at 32 to 33 weeks’ gestation with known fetal maturity, prompt delivery after PPROM is recommended. However, pregnancies at 32 to 33 weeks’ gestation with immature amniotic fluid studies and PPROM are often managed expectantly; antenatal corticosteroids and antibiotic suppression of bacterial organisms are recommended. After antenatal corticosteroids are administered, it is unclear whether delivery or expectant management is associated with lower risks of complications for the mother and fetus.

Patients having PPROM at 23 to 31 weeks’ gestation are usually treated expectantly because of prematurity-associated risks for morbidity and mortality. Antenatal corticosteroid treatment in the presence of PPROM has been found to benefit the infant by reducing the risks of respiratory distress syndrome (20% versus 35%), intraventricular hemorrhage (7.5% versus 16%), and necrotizing enterocolitis (0.8% versus 4.6%); maternal and neonatal infection risks were not different. Adjunctive antibiotics, ampicillin/amoxicillin plus erythromycin, in cases of PPROM before 32 weeks’ gestation prolongs the duration of pregnancy and reduces the risks of neonatal mortality and morbidities (such as infection, cerebral abnormalities, respiratory distress syndrome, necrotizing enterocolitis, bronchopulmonary dysplasia, and patent ductus arteriosus). Although expectant management is the objective in most cases of PPROM before 32 weeks’ gestation, prompt delivery may be necessary when pregnancy is complicated by chorioamnionitis, placental abruption, advanced labor, fetal distress, abnormal presentation with coexisting cervical dilation, human immunodeficiency virus infection, or primary herpes infection.

Management of pregnancies with rupture of membranes before 23 weeks’ gestation is complex because of the high risks for maternal and fetal morbidities and mortality. Maternal risks with PPROM include chorioamnionitis, preterm labor, placental abruption, maternal sepsis, and rarely, death. If management includes prolonged bed rest, muscle wasting, bone demineralization, and venous thrombosis may complicate the course. About 20% of infants born at 25 weeks’ gestation or less after PPROM survive, but nearly all suffer complications of...
extreme prematurity. The risk of lethal pulmonary hypoplasia is about 50% if PPROM occurs before 19 weeks’ gestation and 10% at 25 weeks’ gestation. If PPROM occurs before 25 weeks’ gestation and severe oligohydramnios (<1 cm of amniotic fluid on ultrasonography) persists for more than 14 days, the incidence of lethal pulmonary hypoplasia is nearly 80%. Limb anomalies and other fetal compression findings are frequent as is pulmonary hypertension and hypoxemic respiratory failure; air leaks often complicate the use of positive pressure ventilation in such infants. Because of the high risk for complications of prolonged PPROM before 20 weeks’ gestation, some families choose to terminate the pregnancy.

References:


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American Board of Pediatrics Content Specification(s):

01_Maternal_Fetal: Know the causes, complications, and management of preterm premature rupture of membranes
A 25-year-old woman has a monochorionic twin pregnancy diagnosed at 12 weeks’ gestation. She and her husband are counseled extensively about the outcomes of monochorionic twin gestations. Fetal ultrasonography is repeated at 22 weeks’ gestation. The woman asks if there is ultrasonographic evidence of twin-twin transfusion syndrome.

Of the following, the ultrasonographic finding MOST indicative of twin-twin transfusion syndrome is discordancy of:

- A. amniotic fluid volume
- B. cerebral blood flow velocity
- C. fetal size
- D. umbilical cord size
- E. urinary bladder size

Incorrect:
Correct Answer: A

Twin-twin transfusion syndrome (TTTS) occurs when placental perfusion to monochorionic twins is markedly discrepant: one twin (donor twin) is underperfused and the other (recipient twin) is overperfused. Fetal ultrasonography detects fetal adaptive responses as reflected by a number of findings, most indicative being discordant amniotic fluid volumes. This discordance in amniotic fluid volumes has led to the term twin oligohydramnios-polyhydramnios sequence to describe TTTS.

Twin-twin transfusion syndrome occurs in 10% to 20% of monochorionic twin gestations, and is important because of the high risk of fetal and neonatal mortality (90% if untreated), abnormal growth, and neurologic and developmental morbidity among surviving infants. The true incidence of TTTS is not known because of its wide spectrum of presentations, varying from the vanishing twin phenomenon to unexpected fetal loss during the third trimester.

The diagnosis of TTTS has changed during the past decade. Historically, the definition was based on neonatal criteria: discordance in weight (>20%) and hemoglobin concentration (>5 g/dL [>50 g/L]). With increased use of ultrasonography for fetal assessment, these criteria have been replaced by ultrasonographic criteria. Neonatal
indicators and placental pathologic features remain helpful for the diagnosis of TTTS, especially when ultrasonographic surveillance is not performed. However, neonatal indicators (discrepancies of fetal growth and hemoglobin concentrations) are not specific for TTTS because such discrepancies are also found in monochorionic twins without TTTS.

Several ultrasonographic indicators of TTTS have been identified. Monochorionicity is required, as is sex concordance. Differences in amniotic fluid volumes is a particularly valuable finding because it occurs early in the course of TTTS, is easily identified (maximum vertical pockets of amniotic fluid around the donor and recipient are 2 cm and 8 cm, respectively, during midtrimester), and occurs with both acute and chronic TTTS. Changes in fetal growth, umbilical cord size, urinary bladder size, cerebral blood flow velocity, umbilical artery and ductus venosus Doppler velocimetry, hydrops, and cardiac dysfunction may be present in some, but not all, fetuses with TTTS.

Ultrasonographic and clinical changes in TTTS reflect the degree of placental sharing through various vascular anastomoses that exist in almost all monochorionic twins (Figure).

Figure: Monochorionic placenta, umbilical vessels, surface vascular anastomoses (artery-artery, vein-vein) and deep unpaired anastomosis (artery-vein)

Artery-to-artery and vein-to-vein anastomoses are superficial and protective for regulating excessive blood volume exchange between monochorionic twins. The rate of TTTS is only 5% when an artery-to-artery anastomosis is identified on ultrasonography compared with a rate of 47% to 58% in the absence of an artery-to-artery anastomosis. Placental specimens have identified usually one artery-to-artery anastomosis in 75% of cases of monochorionic twins. This high incidence of artery-to-artery anastomosis partly explains why only 10% to 20% of monochorionic twins develop TTTS.

Artery-to-vein anastomoses are primarily responsible for an unbalanced net blood flow between monochorionic fetuses. Normally, the umbilical artery and umbilical vein at the placenta’s umbilical cord insertion site travel superficially for a distance along the placental surface before diving as a pair deep into the placenta. Within the placenta, the paired artery and vein circulate through the microvascular network where gas exchange occurs. Nutrient- and oxygen-rich blood returns to the fetus by way of the umbilical vein. This unit of gas and nutrient exchange, supplied by the umbilical artery and drained by the umbilical vein, is called a cotyledon. In the abnormal artery-to-vein anastomoses that provide a route for an unbalanced blood flow between fetuses, a single unpaired artery from one fetus supplies a cotyledon that is drained by a single unpaired vein to the other fetus, thus creating an arteriovenous shunt. The presence of unpaired arteries and veins on the surface of the placenta is the hallmark finding of TTTS.

The clinical consequences of an unbalanced blood flow between monochorionic twins differ depending on whether the twin is the donor or recipient. The donor fetus is underperfused; this causes multiple problems including intrauterine growth restriction as well as diminished renal function and subsequent oligohydramnios. Renal tubular degeneration, apoptosis, loss of glomeruli and tubules, and progression to renal dysgenesis have been inconsistently reported. Ultrasonographic findings of difficult-to-visualize urinary bladder, small umbilical cord, and growth restriction are associated with underperfusion of the donor. The donor fetus, in the presence of anhydramnios, also may adhere to the amnion and be crowded by
the recipient fetus’ polyhydramnios to present the ultrasonographic picture of a “stuck twin” that is pushed up against the uterine wall.

Overperfusion of the recipient fetus causes significant hormonal (renin-angiotensin, atrial and brain natriuretic peptides, endothelin), hemodynamic (volume overload, hyperosmolality, hypertension), and biochemical (hypoxemia, acidosis) fetal effects. Overperfusion-associated complications place recipient twins at higher risk than donor twins for fetal death. Subsequent polyuria causes polyhydramnios. More significant, however, are complications of hypervolemia and hypertensive microangiopathy; cardiomyopathy and cardiac dysfunction are the predominant causes of mortality in recipient twins. Recipients also may acquire pulmonary valvular stenosis or atresia because of right ventricular hypertrophy and dysfunction, tricuspid regurgitation, and pulmonary outflow obstruction. The incidence of pulmonary valve stenosis/ataresia is about 10%, or fourfold higher than in monochorionic twins without TTTS. Fetal hydrops, overgrowth, polycythemia, and hypertension also contribute to the precarious status of the recipient twin and the ultrasonographic findings of abnormal Doppler velocimetry, anasarca, umbilical cord edema, relatively large size, and cardiac failure.

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Question 1

You and an obstetric colleague counseled a couple at 21 weeks’ gestation about the treatments and outcomes of monochorionic twins. Amnioreduction was performed at that time. The pregnancy is now at 24 weeks’ gestation. Ultrasonography shows oligohydramnios around the donor twin who appears stuck to the fetal membranes and polyhydramnios around a moderately hydropic recipient twin. Ultrasonography shows no congenital anomalies. Fetoscopic laser ablation of fetal anastomoses is performed.

Of the following, the outcome of twin-twin transfusion syndrome MOST likely in one or both of these twins is:

A. fetal demise
B. neonatal survival
C. neurodevelopmental impairment
D. pulmonary stenosis
E. renal dysplasia

Correct

Twin-twin transfusion syndrome occurs in 10% to 20% of monochorionic twin gestations and, if untreated, is complicated by a high risk of fetal and neonatal mortality (70% to 90%) and growth, neurologic, and developmental morbidity of surviving infants. In the case in the vignette, amnioreduction and laser ablation of placental anastomoses were performed. With such treatment, it is most likely that one or both twins will survive the neonatal period (60%). Neurodevelopmental delay (20% to 50%), pulmonary stenosis (8%), and renal dysplasia (inconsistent reports) occur less frequently.

The number of treatment options to prolong the pregnancy, reduce maternal symptoms, and improve outcomes for twin-twin transfusion syndrome has increased with advances in technology and mastery of procedural skills. Some of the treatment considerations are as follows:

- **Expectant management** is generally indicated for uncomplicated, early or low severity twin-twin transfusion syndrome, especially after 26 weeks’ gestation.
- **Selective fetal reduction** is usually reserved for twin-twin transfusion syndrome after...
failed laser ablation or if complicated by life-threatening problems such as congenital anomalies, severe intrauterine growth restriction (donor) or severe heart failure (recipient) in one twin which places both fetuses at high risk for in utero demise.

- **Septostomy** of the intertwin membrane allows for equilibration of amniotic fluid volumes (relief of oligohydramnios of the donor and polyhydramnios of the recipient) and is most useful for prolonging pregnancies beyond 26 weeks’ gestation. However, amnioreduction is more often applied because of the procedural complexity and complications of septostomy, such as preterm premature rupture of membranes (7%-17%), amniotic fluid leak into the maternal peritoneal cavity (7%), vaginal bleeding [4%], abruptio placentae [2%], and chorioamnionitis (2%).

- **Amnioreduction** has been applied to cases of moderate to severe twin-twin transfusion syndrome at all gestational ages and is especially useful to prolong pregnancies beyond 26 weeks’ gestation. Reducing uterine overdistention acts to lower the risk for preterm labor and preterm premature rupture of membranes. Uteroplacental perfusion is also improved. The procedure is available at nearly all delivery hospitals, relatively inexpensive, and less invasive than most other treatment options.

- **Laser ablation** of placental anastomoses is increasingly recommended for moderate and severe twin-twin transfusion syndrome diagnosed between 16 and 26 weeks’ gestation, and sometimes after amnioreduction has failed. A Cochrane review by Roberts and colleagues included the few randomized trials of interventions for twin-twin transfusion syndrome. Laser ablation was found to have lower rates of neonatal deaths and perinatal deaths and a higher rate of survival without neurologic complications at 6 months of age (Table).

<table>
<thead>
<tr>
<th>Laser vs Amnioreduction</th>
<th>Relative Risk (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal death</td>
<td>0.29 (0.14-0.61)</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>0.59 (0.40-0.87)</td>
</tr>
<tr>
<td>Overall death</td>
<td>0.81 (0.65-1.01)</td>
</tr>
<tr>
<td>Alive without neurologic complications</td>
<td>1.66 (1.17-2.35)</td>
</tr>
</tbody>
</table>

Expectant management is generally preferred over laser ablation in mildly affected twins because of the complications associated with the ablation procedure. Such complications include perforation of the intertwin membrane, amnion-chorion separation, bleeding, and preterm premature rupture of membranes. Laser ablation is only available at select locations because of procedural complexity. Laser ablation is also limited to gestations of 16 to 26 weeks because the use of fetoscopes is restricted by the Food and Drug Administration to this range of gestations. Laser ablation after 26 weeks’ gestation, although available in Canada and some European centers, is under investigation in the United States.

The case in the vignette depicts the use of laser ablation of placental anastomoses after failure of amnioreduction to stabilize the effects of twin-twin transfusion syndrome. Premature delivery and complications of prematurity compound the effects of twin-twin transfusion syndrome on infant outcomes. Short-term outcomes after aggressive amnioreduction as the only treatment modality for twin-twin transfusion syndrome diagnosed before 28 weeks’ gestation was described in 223 sets of twins submitted to the International Amnioreduction Registry. Of these, 346 were live-born twins (78%, 182 recipients and 164 donors). Sixty percent (266 infants) were alive 4 weeks after birth. In approximately half of the cases, both twins survived at least 1 month, and in 158 pregnancies, at least one fetus survived. Ultrasonography of the head before age 4 weeks showed abnormal findings in 25% of the infants (such as intraventricular hemorrhage, ventricular dilation, cerebral echogenic foci, cerebral cysts, and periventricular leukomalacia). Neurologic and developmental assessments after 1.5 to 6 years have been reported in a few infants born after twin-twin transfusion syndrome treated with amnioreduction. The incidence of cerebral palsy ranged from 4.7% to 26%, and severe neurodevelopmental abnormalities ranged from 4% to 8%.

The outcomes of infants who received laser therapy have been reported in a metaanalysis of twin-twin transfusion syndrome. Approximately 20% of pregnancies had no survivors, 30%
had one survivor, and 50% to 60% had two survivors. Neonatal deaths occurred in 4% to 12% of pregnancies and cerebral anomalies in 2% to 33% of surviving twins. Of interest, about 8% of twin-twin transfusion fetuses had nervous system lesions on magnetic resonance imaging before birth. Overall, about 80% of pregnancies resulted in at least one live-born infant and about 60% of infants survived to at least 1 month of age. Neurologic and developmental outcome has been assessed only in a few infant survivors of twin-twin transfusion syndrome whose mothers received laser ablation of placental anastomoses during pregnancy. Much of the morbidity appears to be associated with prematurity, not with donor or recipient status. Normal or mild impairment is reported in about 80% of surviving infants; severe impairment occurs in 11% to 20% of cases (cerebral palsy, hemiparesis, and spastic quadriplegia). Although the mechanisms are not well understood, about 8% of surviving infants have pulmonic valve stenosis; renal dysplasia has been inconsistently reported.

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Question 10

An obstetric colleague asks for your help counseling a 19-year-old primagravida smoker. The patient, now in her third trimester, smokes one pack of cigarettes per day, but is “cutting down.” You meet with the patient and discuss how quitting will benefit her and her fetus.

Of the following, smoking during pregnancy is MOST likely to reduce the risk of:

- A. low birthweight
- B. placental abruption
- C. preeclampsia
- D. preterm rupture of membranes
- E. stillbirth

Correct

Smoking complicates 10% to 18% of pregnancies in the United States, and up to 36% in some regions. Tobacco-smoke exposure during pregnancy, including secondhand smoke, is associated with many increased risks (Table 1). The risk of preeclampsia, however, is lower.

<table>
<thead>
<tr>
<th>Maternal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infertility</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
</tr>
<tr>
<td>Abruptio placenta</td>
</tr>
<tr>
<td>Placenta previa</td>
</tr>
<tr>
<td>Preterm premature rupture of membranes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fetal</th>
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</thead>
<tbody>
<tr>
<td>Hypoxia</td>
</tr>
<tr>
<td>Ischemia</td>
</tr>
<tr>
<td>Miscarriage</td>
</tr>
<tr>
<td>----------------------------------</td>
</tr>
<tr>
<td>Stillbirth</td>
</tr>
<tr>
<td>Perinatal death</td>
</tr>
<tr>
<td>Intrauterine growth restriction</td>
</tr>
<tr>
<td>Decreased heart rate variability</td>
</tr>
</tbody>
</table>

Preeclampsia may be reduced by inhibition of thromboxane A2 production or other immunomodulation. The exact mechanism is unknown, and awaits a fuller explanation of the causes of preeclampsia.

Smoking is associated with lower fertility, increased time to conception, and more difficulties with in vitro fertilization. The risk of ectopic pregnancy is increased. Follicular depletion is facilitated, and gametogenesis is inhibited. Pregnancy loss before 28 weeks’ gestation and stillbirth (loss beyond 28 weeks) are increased in smokers and in nonsmokers exposed to secondhand smoke.

The increased risks in smokers for placenta previa, placental abruption, and preterm rupture of membranes may be related to chronic vascular damage in the placenta and uterus.

Preterm birth is more common in smokers, due in part to the increased risks of premature rupture of the membranes, placental abruption, and placenta previa. Smoking cessation in the first trimester reduces the premature birth rate to that of nonsmokers.

Lower birthweight, an average of 200 to 300 g below the birthweight of newborns not exposed to cigarette smoke, may be caused in several ways. Compared with nonsmokers, the placentas of smokers have thickened intervillous membranes and a reduced capillary volume, reducing oxygen and nutrient transfer to the fetus. Nicotine causes vasoconstriction and decreased blood flow in the uterine and umbilical arteries. Fetal carboxyhemoglobin further reduces oxygen delivery to the fetal tissues. Chronic fetal hypoxia and ischemia, as well as direct cell toxicity from the many chemicals in cigarette smoke, may cause cell damage and trigger inappropriate apoptosis. Smoking cessation in the first trimester mitigates the severity of low birthweight.

Individual studies have suggested links between smoking in pregnancy and facial clefts or digital anomalies. These findings have not been consistently replicated.

Newborns of smokers show signs of stress/withdrawal, such as tremors, poor autonomic regulation, decreased heart rate variability, decreased auditory responsiveness, and an increased need for handling.

The benefits of quitting smoking during pregnancy include reduction or elimination of some of the risks to the fetus. It is estimated that the elimination of maternal smoking would reduce perinatal mortality rates by 5%.

Smokers are able to stop smoking during pregnancy 29% to 46% of the time. Most pregnant smokers who successfully quit smoking have done so by the first prenatal visit. A few more may quit after the first trimester. Many more report reducing the number of cigarettes smoked per day, a strategy that may not eliminate the risks to the fetus. It is speculated that the smoker compensates for the lower number of cigarettes by inhaling more deeply with each one, resulting in a similar total daily dose of nicotine. The relapse rate in the first year after delivery is near 50%.

Quitting smoking is difficult, but a little time invested by the clinician can make a big difference. A program using the “5 As” for treating tobacco dependence (Ask, Advise, Assess, Assist, and Arrange follow-up) is outlined in the Figure and Table 2. The program stresses how limited the time commitment is to the busy clinician (5-15 minutes). A more detailed program, the “5 Rs,” endeavors to overcome the resistance to quitting (Table 3).

**Figure:** The 5 As of smoking cessation (adapted from Fiore and colleagues [2009]).
Table 2: The "5 As" Model for Treating Tobacco Use and Dependence*

<table>
<thead>
<tr>
<th>Action</th>
<th>Duration</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ask</td>
<td>1 minute</td>
<td>Identify and document tobacco use status of every patient at every visit.</td>
</tr>
<tr>
<td>Advise</td>
<td>1 minute</td>
<td>In a clear, strong and personalized manner urge every tobacco user to quit.</td>
</tr>
<tr>
<td>Assess</td>
<td>1 minute</td>
<td>For current tobacco user, is the tobacco user willing to make a quit attempt at this time?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For the ex-tobacco user, how recent did you quit and are there any challenges to remaining abstinent?</td>
</tr>
<tr>
<td>Assist</td>
<td>3 minute</td>
<td>For the patient willing to make a quit attempt, offer medication and provide or refer for counseling or additional behavioral treatment to help the patient quit.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For patients unwilling to quit at this time, provide motivational interventions designed to increase future quit attempts.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For the recent quitter and any with remaining challenges, provide relapse prevention.</td>
</tr>
<tr>
<td>Arrange</td>
<td>1 minute</td>
<td>All those receiving the previous As should receive</td>
</tr>
</tbody>
</table>
follow-up.

* Adapted from Fiore and colleagues (2009).

<table>
<thead>
<tr>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ask parents to consider the personal importance of quitting.</td>
</tr>
<tr>
<td>Advise parents that (1) their personal health will improve (they will feel better physically and perform better in physical activities, they will have fewer wrinkles and their skin will not age as fast, food will taste better, their sense of smell will improve); (2) the children's health will improve (they will have healthier infants and children, they will set a good example for children); (3) their home, car, clothing, and breath will smell better, (4) they will save money, and (5) they will be able to say they are a &quot;former smoker&quot; and can stop worrying about quitting and about exposing others to smoke.</td>
</tr>
<tr>
<td>Try to personalize the benefits of quitting to the parents' situation.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ask parents to identify the negative consequences of tobacco use.</td>
</tr>
<tr>
<td>Highlight the consequences that seem most relevant.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rewards</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ask parents to identify the benefits of quitting.</td>
</tr>
<tr>
<td>Highlight the benefits that seem most relevant.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Roadblocks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Help parents to identify barriers to quitting.</td>
</tr>
<tr>
<td>Identify possible solutions such as pharmacotherapy or changes in daily patterns that may alleviate those barriers.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Repetition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeat the message every time parents who use tobacco visit the office.</td>
</tr>
<tr>
<td>Convey to tobacco users that most people make several quit attempts before they are successful.</td>
</tr>
</tbody>
</table>

* Adapted from Best and colleagues (2009).

The use of drugs to aid smoking cessation during pregnancy, such as nicotine patches or bupropion, is reasonable to consider if nonpharmacologic attempts have been unsuccessful.

**References:**

ACOG Committee on Health Care for Underdeserved Women; ACOG Committee on Obstetric Practice. ACOG Committee Opinion No. 316: Smoking cessation during pregnancy. *Obstet Gynecol* 2005;106:883-888


November


Rayburn WF. Maternal and fetal effects from substance use. Clin Perinatol. 2007;34:559-571

American Board of Pediatrics Content Specification(s):

01_Maternal_Fetal: Know the effects on the fetus and/or newborn infant of maternal substance abuse (eg heroin, cocaine, cannabis, methamphetamines, tobacco)
December

ASSESSMENT PROGRESS: Total Questions: 10  Questions Answered: 2  Correct Answers: 0

Question 2

You are asked to meet with a pregnant woman in preterm labor at 34 weeks’ gestation to discuss her infant’s expected clinical course in case tocolysis is ineffective. The woman’s previous pregnancy was complicated by poorly controlled gestational diabetes and polyhydramnios. Although ultrasonographic imaging during this pregnancy has shown normal amniotic fluid indices, the woman is anxious about developing polyhydramnios. She reports that her diabetes has been well-controlled. You discuss the causes of polyhydramnios, the importance of fetal swallowing in amniotic fluid clearance, and other pathways by which her baby’s amniotic fluid is removed.

Of the following, the MOST effective pathway, after swallowing, for clearance of amniotic fluid is absorption into:

- A. fetal lungs
- B. fetal skin
- C. fetal vessels
- D. maternal circulation
- E. umbilical cord

X Incorrect:

Correct Answer: C

In the absence of any pathologic findings, amniotic fluid (AF) volume is regulated by a balance between production and clearance. During the first trimester of pregnancy, AF arises from a transudate of fetal plasma originating from nonkeratinized fetal skin and a transudate of maternal plasma from uterine decidua and placental tissue. In the second half of gestation, AF is formed primarily from fetal urine production and partly from fetal lung fluid secretion. The addition of dilute fetal urine to the amniotic cavity creates a lower AF osmolality and sodium concentration, causing a divergence in AF composition from that of plasma.

Fetal swallowing is the primary mechanism of clearance of AF from the amniotic cavity. This ability increases with advancing gestational age, with approximately 500 to 1,000 mL removed daily by the term fetus. Interestingly, fetuses may be able to increase their swallowing ability at the end of the third trimester as their mechanisms for thirst and appetite begin to develop.

The second most important pathway for AF clearance occurs by
intramembranous absorption, with direct absorption of AF from the amniotic sac into fetal blood vessels on the fetal surface of the placenta. This pathway is mediated by the osmotic gradient between the AF and fetal blood; water and solutes move from the lower osmolar AF into fetal blood with higher osmolality. Studies in late preterm animals suggest that between 200 and 500 mL of AF can be absorbed into the fetal placental vessels each day. This intramembranous absorption has been shown to increase as much as 10-fold in experimental conditions in sheep fetuses, suggesting the potential of a fetus to regulate this mode of AF clearance. There is indirect evidence for the existence of this intramembranous pathway in humans. For example, injection of $^{51}$Cr into the amniotic cavity of human fetuses with impaired swallowing leads to detection of this tracer in the fetal circulation. An increase in intramembranous absorption is believed to help explain the absence of polyhydramnios in some cases of fetal esophageal obstruction. Flow from AF into the maternal placental circulation, known as transmembranous absorption, has been shown to be small, estimated at 10 mL per day during the third trimester. The Figure summarizes the production and clearance of AF.

A decrease in the amount of fetal urine entering the amniotic cavity will lead to a decrease in AF volume. This may occur if the fetus has renal agenesis, renal obstruction, intravascular depletion, or uteroplacental insufficiency. Studies in sheep fetuses have shown that increases in fetal blood pressure stimulate fetal secretion of atrial natriuretic factor, resulting in diuresis. In contrast, an increase in fetal plasma osmolality stimulates fetal vasopressin secretion in sheep, resulting in an antidiuretic effect. While this suggests that the mature human fetus may be able to respond to intravascular fluid changes by modulating urine flow,
intramembranous absorption is a more effective mechanism of AF clearance. The entry of AF into the fetal lungs does not play a role in intrauterine AF clearance. Although researchers previously hypothesized that fetal lung fluid was derived from inhalation of AF, research established that the source of the fetal lung fluid is the fetal lung itself. Instead of a net movement of AF into the lungs, studies in sheep fetuses have demonstrated that there is a net exit of fetal lung fluid. After the fluid egresses from the lungs, half of the lung fluid is swallowed by the fetus and the remaining half escapes into the amniotic cavity. Indirect evidence of this net outflow of fetal lung fluid is found in humans; with advancing gestation and increased fetal lung maturation, greater amounts of lecithin, a marker of lung maturity, are seen in the AF. Fetal skin and umbilical cord absorption do not play roles in the clearance of AF.

The average AF volume increases during human gestation, with approximately 20 mL present at 10 weeks’ gestation, 630 mL at 22 weeks’ gestation, and 770 mL at 28 weeks. AF volume then remains constant until approximately 39 weeks when there is a sharp decline in AF, with an average of 515 mL at 41 weeks’ gestation. An excess of AF may be related to fetal causes, such as gastrointestinal obstruction and neurologic disorders, or maternal causes, such as poorly controlled diabetes. Because undiagnosed diabetes is one of the most common causes of polyhydramnios in the third trimester, idiopathic polyhydramnios near the end of the pregnancy may prompt retesting for gestational diabetes.

References:


Gilbert WM. Amniotic fluid dynamics. NeoReviews. 2006;7:e292-e299


American Board of Pediatrics Content Specification(s):

04_Respiratory: Know the mechanism of production and factors affecting the clearance of fetal lung liquid, its contribution to amniotic fluid, and its importance to fetal lung development
Question: 9

The obstetrical service at your hospital just began a program in assisted reproductive technology. For the short term, they will be limiting their interventions to in vitro fertilization (IVF), but may expand to other interventions in the future. At a multidisciplinary planning meeting, you are asked about neonatal outcomes after IVF and how the IVF program may affect the neonatal intensive care unit.

Of the following, the outcome of pregnancies resulting from IVF that is MOST similar to that of spontaneously conceived pregnancies is:

- A. dizygous twinning
- B. gestational age at birth
- C. intrauterine growth
- D. monozygous twinning
- E. perinatal mortality

In July 1978, the first infant conceived by means of in vitro fertilization (IVF) was born in the United Kingdom; the first in the United States was born in 1981. Since that time, IVF and other forms of assisted reproductive technology (ART) are associated with more than 1% of births in the United States and more than 1.5% of births in some European countries. Success of the procedure has improved, with 35,785 deliveries yielding 48,756 infants after 122,872 initiated cycles (data from 2003). ART has resulted in about 74% singleton gestations and 26% multiple gestations. Of infants from multiple gestations, the overall rate of three or more fetuses has decreased significantly, but they are still overrepresented compared with the general population (3.2% of IVF pregnancies, 2003).

Following IVF, sometimes more fetuses are discovered than the number of fertilized embryos inserted. Pregnancies resulting from all ART procedures have a two-fold or greater risk for producing monozygotic twins. However, this risk varies based on the technique of ART performed. When performed by in vitro mixing of harvested ova and prepared spermatozoa without further manipulation, IVF produces monozygotic twins at a rate closest to that seen among spontaneous conceptions (0.35% vs 0.4%). Higher rates are reported with other forms of ART such as assisted hatching (0.7%); ovulation induction (1.2%); blast transfer (1.7%); and frozen embryo transfer (3.0%). ART is associated with significantly higher rates of dizygotic twin gestations as well as higher-order multiple gestations than expected from spontaneous conception. Dizygotic twins comprise 95% of twin gestations resulting from ART. In contrast, monozygotic and dizygotic gestations resulting from spontaneously conceived pregnancies are nearly equal (each in the range of about 3.5 per 1,000 live births). More than 50% of twin gestations are born before term, therefore it can be expected that more twins and some higher-order multiple births may need neonatal intensive care services.
Data reveal increased perinatal mortality risk among singletons associated with IVF (odds ratio [OR] = 2.19; 95% confidence interval [CI] = 1.61-2.98). Meta-analyses have demonstrated that singletons associated with IVF have an increased risk of preterm birth (OR = 1.95, 95% CI = 1.73-2.20), low birthweight (OR = 1.77, 95% CI = 1.40-2.22), very low birthweight (OR = 2.70, 95% CI = 2.31-3.14), and intrauterine growth restriction (OR = 1.60, 95% CI = 1.26-2.04). Although not all infants with these characteristics will require intensive care services, each contributes to resource utilization and hospital length of stay. IVF also increases risk of cerebral palsy because of the association with preterm birth (among singletons and multiples), not because of IVF per se.

In vitro fertilization is associated with a higher risk of antepartum hemorrhage than that seen in the overall population. Pregnancies resulting from ART also are significantly more likely to be associated with pre-eclampsia (4.9% vs 2.6%), abruptio placenta (1.1% vs 0.6%), and placenta previa (1.0% vs 0.3%). Induction of labor is more common (OR = 1.5, 95% CI = 1.3-1.6), and more women experience cesarean delivery (OR = 2.1, 95% CI = 1.8-2.4) or an instrument delivery (OR = 2.2, 95% CI = 1.8-2.6). Some infants delivered in these circumstances will require neonatal personnel for delivery room care and some will require intensive care services.

Neonatal intensive care unit admission occurs more often (OR = 1.6, 95% CI = 1.30-1.96) and neonatal mortality is increased (OR = 2.04, 95% CI = 1.23-3.38) following conception with ART. The impact ART will have on a given neonatal unit will obviously be related to the proportion of births resulting from ART and to some degree on the specific ART modalities used.

References


Johnson J, Hartman T, Colby CE. Developmental and genetic outcomes in children conceived through assisted reproductive technologies. NeoReviews. 2006;7:e615-e626. Abstract at: http://neoreviews.aappublications.org/cgi/content/extract/7/12/e615


American Board of Pediatrics Content Specification(s)

Maternal-Fetal Medicine: Know the types of assisted reproductive technologies and how they may influence pregnancy outcome
A 26-year-old primigravid woman in her 24th week of gestation develops regular uterine contractions. Her cervix is closed and measures 4.8 cm in length. Her fetal membranes are intact. She is in good health and her pregnancy thus far has been uncomplicated. Fetal ultrasonography suggests a normally grown fetus with no congenital malformations. The woman is concerned that preterm delivery is imminent and inquires about a test that may determine her chances of giving birth to an extremely preterm infant.

Of the following, the biomarker MOST valuable at predicting spontaneous preterm birth within 7 days is:

A. fetal fibronectin
B. human chorionic gonadotropin
C. placental inhibin A
D. salivary estriol
E. serum corticotropin-releasing hormone

Several markers have been studied and continue to be evaluated for predicting spontaneous preterm birth in human pregnancy. These markers include demographic factors, maternal behaviors, physical characteristics, cervical features, and measurements of specific chemicals in biologic fluids. The latter, termed biomarkers, have been measured in biologic fluids such as amniotic fluid, cervical mucus, vaginal secretions, serum/plasma, urine, and saliva. The long list of biomarkers studied includes activin, adrenocorticotropic, alkaline phosphatase, β₂-macroglobulin, C-reactive protein, corticotropin-releasing hormone, defensin, ferritin, fetal fibronectin, follistatin, granulocyte–colony-stimulating factor, human chorionic gonadotropin, inhibin, interleukin-6, interleukin-10, interstitial cell adhesion molecule-1, lactoferrin, matrix metalloproteinase-9, placental α-fetoprotein, prolactin, relaxin, salivary estriol, and sialidase. Among these biomarkers, to date, fetal fibronectin is the most valuable at predicting spontaneous preterm birth within 7 days of imminent labor.

Fetal fibronectin is a stable glycoprotein with a molecular weight of approximately 450,000 daltons. This glycoprotein is found in the interface between the maternal and fetal components of the choriodecidual junction. Normally, fetal fibronectin is detected in the cervicovaginal mucus during the first 20 weeks of human gestation. It becomes undetectable thereafter until it reappears with emerging spontaneous labor at term. Spontaneous preterm labor is associated with early disruption of the choriodecidual junction, which results in the release of fetal fibronectin in the cervicovaginal mucus. Thus, measuring fetal fibronectin in the cervicovaginal mucus makes a logical approach for predicting spontaneous preterm birth.

Among women presenting with preterm uterine contractions, cervical dilation of up to 3.0 cm, and intact fetal membranes, as the woman in this vignette, the fetal fibronectin assay is the most valuable at predicting spontaneous preterm birth within 7 days. This test is reported to have a high sensitivity of 93%, specificity...
of 82%, positive predictive value of 78%, and negative predictive value of 99%. The greatest clinical value of this test may lie in its negative predictive value, which may exempt women with false labor from the cost and burden of unnecessary treatment of preterm labor. The fetal fibronectin assay is not predictive in the presence of significant vaginal bleeding or after cervical manipulation.

Human chorionic gonadotropin (hCG) is a heterodimer composed of two noncovalently bound peptide subunits, an α subunit containing 92 amino acids and a β subunit containing 145 amino acids. A raised serum concentration of hCG in maternal blood may indicate abnormal placentation or disruption of the chorioideal junction, and it may be associated with an increased risk of adverse pregnancy outcomes including preterm birth. Among women presenting with preterm uterine contractions and intact fetal membranes, a raised concentration of hCG in the cervicovaginal mucus may predict preterm birth within 7 days, with a positive predictive value of 89% and a negative predictive value of 95%. These findings, although suggestive of a possible role for hCG in the clinical setting, remain challenged and unconfirmed by other studies.

Placental inhibin is a dimeric protein that consists of an α subunit and one of two β subunits (βA or βB), forming inhibin A (αβA) or inhibin B (αβB). An abnormal maternal serum concentration of inhibin has been associated with various pregnancy complications. A low maternal serum concentration of inhibin A at an early gestational age is associated with an increased risk of miscarriage, whereas a high maternal serum concentration of inhibin A is associated with fetal Down syndrome. Although promising as a potential biomarker, the value of inhibin A in predicting spontaneous preterm birth before 31 weeks of gestation remains unconfirmed.

Estriol is a major form of circulating estrogen during pregnancy. The concentration of estriol in maternal blood increases linearly throughout pregnancy, but exponentially after 34 weeks of gestation. This surge in the estriol concentration occurs 2 to 4 weeks before the onset of labor at term. Measurement of estriol in maternal saliva correlates with its serum concentration and has been used as a biomarker for predicting spontaneous preterm birth, especially after 34 weeks’ gestation. Its value in predicting spontaneous preterm birth at an earlier gestation, however, remains unestablished. Moreover, the concentration of salivary estriol is influenced by several factors such as diurnal variation, administration of corticosteroids to women in preterm labor, and dietary variations, which potentially limit the clinical use of this assay.

Corticotropin-releasing hormone (CRH) is expressed by the human placenta and the fetal membranes, with the highest level of expression during the third trimester of pregnancy. Among women presenting with preterm uterine contractions, maternal serum CRH concentration has been found to be higher in women who deliver within 24 hours of onset of labor compared with women whose delivery is delayed beyond 24 hours. When stratified by gestational age at the time of presentation, however, this difference in maternal serum CRH concentration between groups is statistically insignificant at a gestational age of less than 28 weeks. Thus, the value of maternal CRH in predicting spontaneous preterm birth at an earlier gestation remains questionable. Moreover, the concentration of maternal CRH is influenced by factors such as infection and administration of tocolytic drugs, which potentially limit the clinical use of this assay.

### References


### American Board of Pediatrics Content Specification(s)

Maternal-Fetal Medicine: Know the physiologic and molecular biological characteristics of normal labor and parturition

Maternal-Fetal Medicine: Know the risk factors, including the effects of choriodecidual infection and inflammation as contributing factors, for preterm labor
Question: 2

A relative of yours and her husband, both healthy adults ages 29 and 31 years, respectively, have had difficulty in conceiving a child. Eight months ago, they sought consultation with an infertility specialist but to date no testing other than physical examinations and cycle-timing have been performed. Before starting any assisted reproductive interventions, the couple now has conceived.

Of the following, the GREATEST risk for this spontaneously conceived infant is:

- A. aneuploidy
- B. imprinting defects
- C. monozygotic twinning
- D. perinatal mortality
- E. post-term delivery

In the United States, more than 1% of infants are conceived with the use of assisted reproductive technology (ART). In 2006, 126,726 ART procedures were performed in the United States. Of the families seeking evaluation for infertility, some conceive spontaneously, but the exact number of such pregnancies is unknown. It is presumed that many of these spontaneous pregnancies occur in couples who experience transient infertility (e.g., failure to conceive after 1 year of unprotected intercourse). These couples are described as being subfertile and many recover without intervention. It is estimated that one in seven couples experience subfertility; half of these couples will conceive a pregnancy spontaneously.

Maternal and neonatal outcome data are available for pregnancies complicated by transient infertility as in the couple in the vignette and for those pregnancies conceived by means of ART. Perinatal mortality is significantly greater in pregnancies occurring in subfertile women whose infertility is untreated than in pregnancies in the general population (odds ratio [OR] = 3.3, 95% confidence interval [CI] = 1.6-6.8). Studies comparing subfertile women with women experiencing no difficulty in getting pregnant have shown subfertile women to be older (31 years vs 27 years) and more likely primiparous (70% vs 65%). After adjusting for these differences, several pregnancy and birth complications are more often seen in subfertile mother/fetus dyads (Table 1).

Although aneuploidy has been associated with repeated pregnancy losses, especially early in gestation, chromosomal number is not shown to be affected by a history of subfertility. In general, infants conceived via most forms of ART have not been shown to have increased risk of aneuploidy. Among pregnancies resulting from intracytoplasmic sperm injection, chromosomal abnormalities have been found in 1.6% of cases (vs 0.5% of controls) and inherited congenital anomalies are found in 1.4% of cases (vs 0.3% to 0.4%...
of controls). Likewise, imprinting defects associated with hypomethylation, including Beckwith-Wiedemann syndrome and Angelman syndrome, have an increased prevalence among infants conceived with ART. Fetal genetic testing may be recommended for pregnancies conceived by intracytoplasmic sperm injection but not necessarily for pregnancies conceived through other ART methods or occurring spontaneously in subfertile women, as in the woman in the vignette.

Multifetal gestation is seen in about 26% of pregnancies conceived using ART. The rate of monozygotic twinning is dependent on the form of ART used. IVF produces monozygotic twins at a rate closest to that seen among spontaneous conceptions (0.35% vs 0.4%). Higher rates are reported with other forms of ART such as assisted hatching (0.7%); ovulation induction (1.2%); blast transfer (1.7%); and frozen embryo transfer (3.0%). Spontaneously conceived pregnancies, including those in subfertile couples, exhibit no increase in monozygotic twinning. Although post-term pregnancy has not been associated with subfertility, a number of newborn conditions have been shown to be more common among neonates delivered to women with subfertility (Table 2).

References


Johnson J, Hartman T, Colby CE. Developmental and genetic outcomes in children conceived through assisted reproductive technologies. NeoReviews. 2006;7:e615-e626. Abstract at: http://neoreviews.aappublications.org/cgi/content/extract/7/12/e615?


American Board of Pediatrics Content Specification(s)

Maternal-Fetal Medicine: Know the types of assisted reproductive technologies and how they may influence pregnancy outcome

Maternal-Fetal Medicine: Know the types of multiple gestation and the effects on the mother of multiple gestation pregnancy

Genetics/Dysmorphism: Know the components of a complete family history for genetic disorders
A 32-year-old white woman in her third pregnancy seeks consultation at approximately 22 weeks of gestational age. Her first pregnancy, 4 years earlier, was complicated by spontaneous placental abruption at 30 weeks of gestational age that led to cesarean section birth of a 1,284-g infant. Her second pregnancy, 2 years earlier, was complicated by spontaneous premature rupture of membranes at 27 weeks of gestational age that led to a repeat cesarean section birth of a 902-g infant. Her current pregnancy thus far has been uncomplicated except for mild intermittent uterine contractions. Her cervix is closed and fetal membranes are intact. The woman is in good health except for cigarette smoking which she has continued throughout pregnancy. Fetal ultrasonography reveals a normally grown singleton fetus with no congenital malformations. The woman is concerned that another preterm birth is imminent and inquires about its causes.

Of the following, the MOST common cause of preterm birth is:

- A. genetic predisposition
- B. maternal/fetal indications
- C. premature rupture of membranes
- D. spontaneous preterm labor
- E. substance abuse

Preterm birth is defined as birth that occurs before 37 weeks of gestation. Approximately 5% of preterm births occur at less than 28 weeks (designated as extreme prematurity), 15% at 28 to 31 weeks (severe prematurity), 20% at 32 to 33 weeks (moderate prematurity), and 60%...
at 34 to 36 weeks (late prematurity) of gestation.

The causes of preterm birth are classified into three categories: spontaneous preterm labor with intact membranes (approximately 45% of cases), premature rupture of membranes (30%), and preterm delivery for maternal/fetal indications (25%). Births that follow spontaneous preterm labor and premature rupture of membranes together are designated as spontaneous preterm births. Spontaneous preterm birth is most commonly caused by preterm labor in white women, but by premature rupture of membranes in black women.

Preterm labor is defined as regular uterine contractions accompanied by cervical change before 37 weeks of gestation. Spontaneous preterm labor with intact membranes is initiated by multiple mechanisms, including infection or inflammation, uteroplacental ischemia or hemorrhage, uterine overdistention, and immune-mediated processes. Several risk factors contribute to the transition from uterine quiescence to preterm labor (Table).

Premature rupture of membranes is defined as spontaneous rupture of fetal membranes before 37 weeks of gestation at least 1 hour before the onset of uterine contractions. The cause of membrane rupture in most cases is unknown, but asymptomatic intrauterine infection is a frequent precursor. Risk factors for premature rupture of membranes are similar to those for spontaneous preterm labor with intact membranes, but intrauterine infection, bacterial vaginosis, and tobacco exposure play important roles.

As reported by the National Institutes of Child Health and Human Development Maternal-Fetal Medicine Units Network, preterm delivery for maternal/fetal indications, in which labor is either induced or the infant is delivered by prelabor cesarean section, accounts for approximately 25% of preterm singleton births. Among these preterm deliveries, the indications are preeclampsia in approximately 50% of cases, fetal distress in 25%, and fetal growth restriction, placental abruption, or fetal death in the remainder.

The recurrent, familial, and racial patterns of preterm birth suggest that genetic predisposition may play a causal role. The proposed candidate genes with potential implications for spontaneous preterm labor or premature rupture of membranes include those related to progesterone receptor, β₂-adrenergic receptor, decidual relaxin, fetal mitochondrial proteins, and inflammatory cytokines such as interleukin-1 and tumor necrosis factor α. To date, the associations between polymorphisms in candidate genes and the risk of preterm birth have been modest at best. Genome-wide association studies now in progress may provide new insights in the gene-gene and gene-environment interactions related to preterm birth.

Substance abuse during pregnancy ranges from 0.4% to 27%, depending on the population surveyed. The drugs involved include alcohol, amphetamines, barbiturates, benzodiazepines, cocaine, heroin, marijuana, and opiates. In the United States, approximately 20% to 25% of pregnant women smoke, and among these, 12% to 15% continue to smoke throughout pregnancy. Tobacco use increases the risk of preterm birth (less than twofold) after adjusting for other factors. Likewise, most drugs, including heavy alcohol consumption, are associated with an increased risk of preterm birth.

**Suggested Readings**


Goldenberg RI, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth.


**American Board of Pediatrics Content Specification(s)**

Maternal-Fetal Medicine: Know the risk factors, including the effects of choriodecidual infection and inflammation as contributing factors, for preterm labor

Maternal-Fetal Medicine: Know the effects on the fetus and/or newborn infant of maternal substance abuse (e.g., heroin, cocaine, cannabis, methamphetamines, tobacco)

Maternal-Fetal Medicine: Know the effects on the fetus and/or newborn infant of maternal alcohol use

Maternal-Fetal Medicine: Know the causes, complications, and management of preterm premature rupture of membranes

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# Table: Common Risk Factors for Preterm Labor

<table>
<thead>
<tr>
<th>Maternal Characteristic</th>
<th>Risk Factors</th>
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<tbody>
<tr>
<td>Demographics</td>
<td>Black race</td>
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<td></td>
<td>Low socioeconomic and educational status</td>
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<td>Young or advanced maternal age</td>
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<td>Single marital status</td>
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<td>Short stature</td>
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<td>Nutrition</td>
<td>Low prepregnancy body mass index</td>
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<td>Deficiency of iron, folate, zinc, or vitamin C</td>
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<td>Health</td>
<td>Psychological and physical stress</td>
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<td>Depression</td>
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<td>Intrauterine infection</td>
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<td>Adverse behaviors: smoking, substance abuse</td>
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<td>Physical abuse</td>
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<td>Pregnancy history</td>
<td>Short interpregnancy interval</td>
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<td></td>
<td>Prior preterm birth</td>
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<tr>
<td>Current pregnancy characteristics</td>
<td>Multiple gestation</td>
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<td></td>
<td>Placental abruption or previa</td>
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<td></td>
<td>Extremes in amniotic fluid volume (polyhydramnios, oligohydramnios)</td>
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<td>Uterine anomalies</td>
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<td>Cervical abnormalities</td>
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</table>
Question: 9

At 11 weeks’ gestation, ultrasonography confirms a twin gestation. Assessment of chorioicnity and fetal membranes suggests monozygosity.

Of the following, the feature MOST unique to monozygotic twinning is:

- A. acardiac anomaly
- B. chimerism
- C. dichorionic placentation
- D. fetus papyraceus
- E. vascular anastomoses

Spontaneous twin gestation occurs in approximately 1 in 80 live births. Monozygotic twins result from fertilization of one ovum that subsequently divides, and dizygotic twins result from the fertilization of two ova by different sperm. Worldwide, the rate of monozygotic twinning is fairly constant, but variability in the rate of dizygotic twinning results in ethnic and geographic differences in overall rates of twinning.

Twin placentae may be monochorionic or dichorionic and zygosity may be inferred from this distinction. With rare exception, monochorionic placentae are monozygotic. Dichorionic placentae may be monozygotic or dizygotic. Dizygotic twins are dichorionic and diamniotic, but may have a single, fused placenta. In contrast, monozygotic twins may be dichorionic or monochorionic, and all monochorionic twins are monozygotic. Monochorionic twins may be diamniotic or monoamniotic (Figure 1).

The timing of the twinning event determines placental conformation. Zygotic separation
between days 0 and 3 of gestation results in dichorionic placenta. Separation between days 4 and 7, following formation of the chorion, results in monochorionic placenta. The amnion begins to form between days 6 and 8, and separation between days 8 and 14 results in monochorionic monoamniotic placenta. Conjoined twins represent a rare form of monozygotic twinning and must arise after day 14 of gestation when the primitive streak has begun to form.

The frequency of twinning according to placental membranes is shown in the Figure 2. Approximately one third of twin gestations are monozygotic. Most monozygotic twins are also monochorionic and diamniotic (70%-75%) and fewer are dichorionic diamniotic (25% to 30%). Only 1% of twins are both monozygotic and monoamniotic.

An excess of females are observed to have monozygotic twinning. Also, there is a decreasing incidence of male twin pairs from early to late embryonic separation. The smallest excess in females is observed in dichorionic monozygotic twins and the highest excess in conjoined twins. Skewed X-chromosome inactivation may explain this observation.

Up to 70% of monochorionic twins have placental vascular connections. Arterial to arterial connections are most common and allow blood to shunt from one side to the other, equalizing pressure and volume. Large-caliber interfetal anastomoses may lead to significant shunts and vascular compromise or imbalance. The arterial-to-venous shunt is not a direct communication, but occurs when one cotyledon is fed by the artery of one twin and drained by vein into the other twin. A shared cotyledon, when not accompanied by artery-to-artery or vein-to-vein anastomoses, allows one twin to drain into the other and results in twin-to-twin transfusion syndrome (TTTS) and hemodynamic compromise. TTTS occurs in up to 30% of monochorionic twins and more commonly in diamniotic twins than monoamniotic twins. Congenital anomalies are more prevalent in infants with TTTS, particularly congenital heart defects such as ventricular septal defects, atrial septal defects, and pulmonary stenosis. TTTS-associated congenital heart disease predominantly affects the recipient twin. Dizygotic twins with a fused placenta may experience small asymptomatic vascular connections.

Twin reversal arterial perfusion (TRAP) sequence or acardiac anomaly is unique to monozygotic monochorionic twins (1% of cases), and occurs when a superficial artery-to-artery placental anastomosis allows a structurally normal twin to perfuse a cotwin who is lacking a well-formed cardiac structure. Circulation of the acardiac twin is reversed and the acardiac twin is hemodynamically dependent on the pump twin. Because of preferential perfusion of the lower body, the acardiac twin usually is accephalic with poorly formed upper extremities and frequently lacks other structures. The mechanism causing TRAP sequence is unclear, and may relate to aberrant placental vasculature with circulatory reversal and subsequent abnormal cardiac development. On the other hand, acardia may represent abnormal cardiac embryogenesis with secondary development of an aberrant circulatory pattern.

Fetus papyraceus is the consequence of the early demise of one twin. The process of gradual absorption of the fluid in the dead twin’s tissues, disappearance of amniotic fluid, and compression of the fetus incorporates the fetus into the membranes. Fetus papyraceus is also known as fetus compressus and membranous twin. Fetus papyraceus occurs in both dizygotic and monozygotic twins. Cutis aplasia in the surviving twin has been associated with fetus papyraceus.

Chimerism is the presence of different populations of genetically distinct cells that originated in different zygotes. Chimerism is a rare occurrence in dizygotic twins and is evidenced by individual blood group or lymphocytic karyotype analyses that demonstrate genetically dissimilar cell types. Blood chimerism in dizygotic twins is explained by transplacental anastomoses that allow migration of blood cell precursors from one twin to the other twin. Also possible is fetal-maternal-fetal chimerism, as often
Dizygotic placentas show no obvious vascular connection. The graft is well tolerated by the host fetus because the transfer occurs so early in embryonic life.

Congenital anomalies occur more commonly in twins than singletons. Monozygotic twins have the highest incidence of structural defects (approximately 10% of live born monozygotic twins) and these anomalies are most often discordant. Midline malformations, such as cloacal anomalies and neural tube defects, may be part of the twinning process. Congenital heart defects may be associated with placental vascular connections and fluctuations in blood flow early in cardiogenesis. Disruptions, such as limb reductions, may be related to sharing of placental circulations. Deformations, such as clubbed foot, may be the result of constraint and intrauterine crowding. Mirror-image twinning, evidenced by inverse laterality, occurs in 10% to 15% of monozygotic twins. Situs inversus is not usually a feature of mirror image twinning, rather minor features such as tooth eruption, cowlicks, and handedness are on opposite sides.

Compared with singletons, twins experience a sixfold greater perinatal mortality rate, with fetal demise occurring in up to 8% of twins. Risk is largely related to chorionicity, with monozygotic twins at risk for malformations and complications associated with monochorionic placentation. Hemodynamic imbalances, growth restriction, and abnormal cord insertion occur more frequently when placentation is monochorionic. Perinatal mortality is highest for monoamnionic twins (50%-60%) and is influenced by their unique risk of umbilical cord entanglement. Monochorionic diamniotic twins have perinatal mortality rates approximating 25%, and largely attributed to TTTS. Perinatal mortality in dichorionic monozygotic twins approaches 9%, and is largely attributed to congenital anomalies.

**Suggested Readings**


**American Board of Pediatrics Content Specification(s)**

Maternal-Fetal Medicine: Know the types of multiple gestation and the effects on the mother of multiple gestation pregnancy

Maternal-Fetal Medicine: Know the normal morphologic development of the placenta

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**Figure 1.**

**A,** Dichorionic, diamniotic twinning.  **B,** Monochorionic, diamniotic twinning.  **C,** Monochorionic, monoamniotic twinning.

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**Question: 9**

At 11 weeks’ gestation, ultrasonography confirms a twin gestation. Assessment of chorionicity and fetal membranes suggests monozygosity.

Of the following, the feature MOST unique to monozygotic twinning is:

- A. acardiac anomaly
- B. chimerism
- C. dichorionic placentation
- D. fetus papyraceus
- E. vascular anastomoses
Figure 2.

Frequency of twinning according to placental membranes.

TWINNING

Monozygotic 33.3%

Monochorionic

Dichorionic

Diamniotic 25%-30%

Dizygotic 66.6%

Dichorionic Diamniotic

Monochorionic

Diamniotic 70%-75%

Monoamniotic 1-2%

Question: 9

At 11 weeks' gestation, ultrasonography confirms a twin gestation. Assessment of chorionicity and fetal membranes suggests monozygosity.

Of the following, the feature MOST unique to monozygotic twinning is:
Question: 5

A 1,500-g male infant born at 32 weeks' gestation is brought to your nursery with respiratory distress. A blood gas analysis shows a carboxyhemoglobin concentration of 5%. After you attend to the child, you talk with the obstetrician and find that the mother is a 19-year-old primigravida cigarette smoker. You go to see the mother in her hospital room to talk to her and her family. The maternal grandmother is an epidemiologist. She engages you in a discussion about the risks to the child, from exposure to smoking during the mother's pregnancy and later to secondhand smoke.

Of the following, secondhand smoke exposure in childhood, compared with smoking in pregnancy, is MOST clearly associated with:

- A. adolescent tobacco use
- B. childhood cancer
- C. hyperactivity
- D. obesity
- E. wheezing illnesses

Tobacco smoke exposure during pregnancy is associated with many increased risks to the child in later life. Table 1 lists these risks, classified by the strength of the association. After birth, exposure to secondhand smoke can worsen some of these risks and add other risks. Confounding factors make it difficult to know if prenatal or postnatal exposure is the more important factor for a given risk.

Table 1: Health Consequences of Fetal Exposure to Tobacco Smoke *

<table>
<thead>
<tr>
<th>Causal relationship</th>
<th>Associated, suggestive of causal relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low birthweight</td>
<td>Preterm delivery</td>
</tr>
<tr>
<td>Sudden infant death</td>
<td>Middle-ear disease</td>
</tr>
<tr>
<td>Asthma</td>
<td>Acute otitis media</td>
</tr>
<tr>
<td>Lower respiratory illnesses</td>
<td>Recurrent otitis media</td>
</tr>
<tr>
<td>Lower level of lung function</td>
<td>Chronic middle ear effusion</td>
</tr>
<tr>
<td></td>
<td>Cough and wheezing illnesses</td>
</tr>
<tr>
<td></td>
<td>Cancer</td>
</tr>
<tr>
<td></td>
<td>Leukemia</td>
</tr>
</tbody>
</table>

*
A few studies have been able to distinguish the effects of prenatal from postnatal exposure. Of the health consequences listed in the vignette, hyperactivity emerges as being more frequently associated with postnatal exposure than with prenatal exposure. Other consequences more often associated with postnatal smoking exposure include sickle cell crisis and death from fire. Table 2 categorizes the health consequences of maternal smoking as those caused mainly by postnatal smoking, those caused by either prenatal or postnatal smoking, and those that have significant uncertainty as to whether prenatal or postnatal smoking contributes more.

Table 2: Health Consequences of Maternal Smoking: Associations With Postnatal and Either Prenatal or Postnatal Exposures*

<table>
<thead>
<tr>
<th>Postnatal smoking alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperactivity</td>
</tr>
<tr>
<td>Sickle cell crisis</td>
</tr>
<tr>
<td>Fire-related death</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Either prenatal or postnatal smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden infant death syndrome</td>
</tr>
<tr>
<td>Lower respiratory illnesses</td>
</tr>
<tr>
<td>Cough, wheeze, or asthma</td>
</tr>
<tr>
<td>Middle-ear disease</td>
</tr>
<tr>
<td>Decreased lung function</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Uncertainty about contributions of prenatal and postnatal smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolescent tobacco use</td>
</tr>
<tr>
<td>Childhood cancer</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Atherogenesis</td>
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<tr>
<td>Type 2 diabetes</td>
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</tbody>
</table>

* Adapted from Best and colleagues (2009) and Twaedella and colleagues (2010).

Animal and human studies have shown that prenatal smoking can cause structural and functional changes to the upper and lower respiratory system and the immune system. A lower average birthweight and smaller airways are also associated with prenatal tobacco use. Such changes may lead to an increase in childhood wheezing illnesses and middle-ear disease, and lower levels of lung function.

Similarly, lasting changes to the autonomic nervous system, especially the cholinergic system, have been demonstrated in smoke-exposed animal fetuses. It has been suggested that the toxic effects of maternal tobacco smoking on the rapidly growing fetal central nervous system has other lasting effects. Lower verbal scores on the Bayley Scales of Infant Development, more aggression and oppositional behavior as an adolescent, and increased risk for tobacco use as an adolescent are associated with in utero smoking exposure. These associations remain after regression analysis for postnatal factors such as parental smoking or poverty.

Sudden infant death syndrome appears to be more influenced by prenatal nicotine exposure than by postnatal secondhand smoke, but the exact mechanism is not well understood.

Some childhood cancers are associated with prenatal and postnatal smoking exposure, again without clear evidence as to which exposure is more important. A recent report of the Surgeon General concluded that the evidence to date, “...is suggestive but not sufficient to infer a causal relationship.”

Obesity in childhood, atherogenesis in adulthood, and type 2 diabetes are associated with smoking exposure. Studies disagree about the relative importance of prenatal and postnatal smoking exposure with these outcomes.

**References**


Best D; Committee on Environmental Health, Committee on Native American Child Health, Committee on


**American Board of Pediatrics Content Specification(s)**

Maternal-Fetal Medicine: Know the effects on the fetus and/or newborn infant of maternal substance abuse (eg heroin, cocaine, cannabis, methamphetamines, tobacco)
A 35-year-old black woman who is 5 feet (152 cm) tall and weighs 99 lbs (45 kg) becomes pregnant following stimulation of ovulation and artificial insemination. Six weeks after conception, ultrasonographic examination shows the fetal crown-rump length to be below the 10th percentile for 8 weeks’ postmenstrual age. Maternal blood pressure is 120/90 mm Hg, and her hemoglobin concentration is 12.4 g/dL (124 g/L). She admits to smoking about 1 cigarette per week and consuming a glass of wine with dinner 3 to 5 days per week. She had been taking no dietary or vitamin supplements. Chorionic villus sampling demonstrates normal fetal karyotype: 46,XY.

Of the following, the first trimester fetal growth restriction for this fetus is MOST closely related to maternal:

- A. age
- B. alcohol consumption
- C. anthropometrics
- D. blood pressure
- E. race

First trimester fetal growth commonly is used for gestational assessment because of its relative accuracy compared with observations made later in pregnancy. As seen with all biological measurements, variation from normative values may be associated with normal growth factors or with noxious influences. In this vignette, gestational age is accurately known, eliminating a common factor influencing fetal growth evaluation in general. First trimester fetal growth has been shown to be positively associated with maternal age, black race, and male sex. Of the factors listed, only maternal diastolic blood pressure elevation is related to first trimester fetal growth restriction.

Shorter crown-rump length in first trimester fetuses is associated with elevated maternal diastolic blood pressure, higher hematocrit or hemoglobin concentrations, smoking, and nonuse of folic acid supplementation. Early pregnancy diastolic hypertension, in addition to its effect on first trimester fetal size, also affects the incidence of later, placental conditions such as preeclampsia and intrauterine fetal growth restriction. Although the exact mechanism is uncertain, higher hemoglobin concentrations may represent lower circulating maternal blood volume and reduced utero-placental perfusion. Mothers who smoke have a higher incidence of fetal first trimester growth restriction than nonsmokers. When the number of cigarettes per day is evaluated, higher cigarette use is associated with a trend toward more adverse growth effect.

Folic acid is an important factor influencing cell division, apoptosis, and methylation of DNA. A strong interaction is found between the combination of smoking and nonuse of folic acid supplementation and first trimester fetal growth restriction. Coelomic fluid folic acid concentrations are lower in smokers than in nonsmokers, suggesting a negative effect of smoking on the bioavailability of folic acid in the fetus. Later in pregnancy, maternal smoking is associated with reduced placental blood flow and with intrauterine growth restriction.
Maternal weight has been shown to be positively associated with fetal weight later in pregnancy, but maternal anthropometrics are not related to first trimester fetal size. The associations between fetal first trimester growth and pregnancy outcome have been similar in studies of spontaneous pregnancy and of pregnancy following assisted reproductive techniques. Alcohol consumption is found to be unrelated to first trimester fetal growth restriction.

First trimester fetal growth restriction has been associated with increased risks of neonatal mortality and morbidity including prematurity (adjusted odds ratio [AOR], 2.12, 95% confidence interval [CI, 1.24-3.61), intrauterine growth restriction (AOR, 2.64; 95% CI, 1.64-4.25), and low birthweight (AOR, 2.42; 95% CI, 1.41-4.16). Infants delivered after first trimester fetal growth restriction have been shown to demonstrate compensatory acceleration in postnatal growth for the first 2 years. Longer follow-up studies are needed to determine if this growth acceleration is a harbinger of cardiovascular or metabolic disease(s) later in childhood or adult life.

**References**

First-trimester determination of complications of late pregnancy. *JAMA*. 2010;303:561-562


Rogers EE, Piecuch RE. Neurodevelopmental outcomes of infants who experience intrauterine growth restriction. *NeoReviews*. 2009;10:e100-e112. Accessed April 27, 2010 at: [http://neoreviews.aappublications.org/cgi/content/full/10/3/e100](http://neoreviews.aappublications.org/cgi/content/full/10/3/e100)

**American Board of Pediatrics Content Specification(s)**

Maternal-Fetal Medicine: Know the general principles, applications, and limitations of ultrasonography, including Doppler blood flow measurements, in assessment of fetal conditions and well-being

Maternal-Fetal Medicine: Know how to use obstetric and ultrasonographic data to determine gestational age, and know their limitations

Maternal-Fetal Medicine: Know how to evaluate fetal growth rate and fetal growth restriction and the management of fetal growth restriction

Nutrition: Know the maternal, placental, and fetal factors that affect intra-uterine fetal growth

Nutrition: Know the postnatal growth patterns of SGA infants

Nutrition: Know how extremes of intrauterine growth affect postnatal nutritional requirements