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Cloherty and Stark's Manual of Neonatal Care

8TH EDITION

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1
Fetal Assessment and Prenatal Diagnosis

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KEY POINTS

- Several different methods for prenatal diagnosis of fetal disease are currently available to the clinician.
- Fetal size and growth rate abnormalities may have significant implications for perinatal prognosis and care.
- Methods to assess fetal well-being prenatally and perinatally are central to obstetrical practice.

I. GESTATIONAL AGE ASSESSMENT is important to both the obstetrician and pediatrician and must be made with a reasonable degree of precision. Elective obstetric interventions such as chorionic villus sampling (CVS) and amniocentesis must be timed appropriately. When premature delivery is inevitable, gestational age is important with regard to prognosis, the management of labor and delivery, and the initial neonatal treatment plan.

A. The clinical estimate of gestational age is usually made on the basis of the first day of the last menstrual period (LMP). Accompanied by physical examination, auscultation of fetal heart sounds and maternal perception of fetal movement can also be helpful.

B. Ultrasound is the most accurate method for estimating gestational age. During the first trimester, fetal crown-rump length (CRL) can be an accurate predictor of gestational age. At <8 weeks and 6 days if the CRL and the LMP are >5 days different, the ultrasound is the best estimate for gestational age. From 9 0/7 to 15 6/7 weeks, CRL estimation of gestational age is expected to be within 7 days of the true gestational age. After 14 weeks, measurements of the biparietal diameter (BPD), the head circumference (HC), abdominal circumference (AC), and the fetal femur length best estimate gestational age. Strict criteria for measuring the crosssectional images through the fetal head ensure accuracy. Nonetheless, owing to normal biologic variability, the accuracy of gestational age estimated by biometry decreases with increasing gestational age. For measurements made at 16 to 21 6/7 weeks of gestation, the variation is up to 10 days; at 22 to 27 6/7 weeks, the variation is up to 14 days; and at 28 weeks and beyond, the variation can be up to 21 days.

II. PRENATAL DIAGNOSIS OF FETAL DISEASE continues to improve. The genetic or developmental basis for many disorders is emerging, along with increased test accuracy. Two types of tests are available: screening tests and diagnostic procedures. Screening tests, such as a sample of the mother's blood or an ultrasound, are noninvasive but relatively nonspecific. A positive screening test, concerning family history, or an ultrasonic examination that suggests anomalies or aneuploidy may lead patient and physician to consider a diagnostic procedure. Diagnostic procedures, which necessitate obtaining a sample of fetal material, pose a small risk to both mother and fetus but can confirm or rule out the disorder in question.

A. Screening by maternal serum analysis during pregnancy individualizes a woman's risk of carrying a fetus with a neural tube defect (NTD) or an aneuploidy such as trisomy 21 (Down syndrome) or trisomy 18 (Edward syndrome).

1. Maternal serum α-fetoprotein (MSAFP) measurement between 15 and 22 weeks' gestation screens for

NTDs. MSAFP elevated above 2.5 multiples of the median for gestation age occurs in 70% to 85% of fetuses with open spina bifida and 95% of fetuses with anencephaly. In half of the women with elevated levels, ultrasonic examination reveals another cause, most commonly an error in gestational age estimate. Ultrasonography that incorporates cranial or intracranial signs such as changes in head shape (lemon sign) or deformation of the cerebellum (banana sign) that are secondary to the NTD increase the sensitivity of ultrasound for the visual detection of open spinal defects.

2. Second-trimester aneuploidy screening: MSAFP/quad panel. Low levels of MSAFP are associated with chromosomal abnormalities. Altered levels of human chorionic gonadotropin (hCG), unconjugated estriol (uE3), and inhibin are also associated with fetal chromosomal abnormalities. On average, in a pregnancy with a fetus with trisomy 21, hCG and inhibin levels are higher than expected and uE3 levels are decreased. A serum panel in combination with maternal age can estimate the risk of trisomy 21 for an individual woman. For women <35 years, 5% will have a positive serum screen, but the majority (98%) will not have a fetus with aneuploidy. Only 80% of fetuses with trisomy 21 will have a "positive" quad screen (MSAFP, hCG, uE3, inhibin). Trisomy 18 is typically signaled by low levels of all markers.

3. First-trimester serum screening. Maternal levels of two analytes, pregnancy-associated plasma protein-A (PAPP-A) and hCG (either free or total), are altered in pregnancies with an aneuploid conception, especially trisomy 21. Similar to second-trimester serum screening, these values can individualize a woman's risk of pregnancy complicated by aneuploidy. However, these tests need to be drawn early in pregnancy (optimally at 9 to 10 weeks) and, even if abnormal, detect less than half of the fetuses with trisomy 21.

4. First-trimester nuchal lucency screening. Ultrasonographic assessment of the fluid collected at the nape of the fetal neck is a sensitive marker for aneuploidy. With attention to optimization of image and quality control, studies indicate a 70% to 80% detection of aneuploidy

in pregnancies with an enlarged nuchal lucency on ultrasonography. In addition, some fetuses with structural abnormalities such as cardiac defects will also have an enlarged nuchal lucency.

5. Combined first-trimester screening. Combining the two first-trimester maternal serum markers (PAPP-A and β-hCG) and the nuchal lucency measurements in addition to the maternal age detects 80% of trisomy 21 fetuses with a low screen positive rate (5% in women <35 years). This combined first-trimester screening provides women with a highly sensitive risk assessment in the first trimester.

6. Combined first- and second-trimester screening for trisomy 21. Various approaches have been developed to further increase the sensitivity of screening for trisomy 21 while retaining a low screen positive rate. These approaches differ primarily by whether they disclose the results of their first trimester results.

a. Integrated screening. This is a nondisclosure approach that achieves the highest detection of trisomy 21 (97%) at a low screen positive rate (2%). It involves a first-trimester ultrasound and maternal serum screening in both the first and second trimester before the results are released.

b. Sequential screening. Two types of sequential screening tools exist. Both are disclosure tests, which means that they release those results indicating a high risk of trisomy 21 in the first trimester but then go on to either further screen the entire remaining population in the second trimester (stepwise sequential) or only a subgroup of women felt to be in a medium-risk zone (contingent sequential). With contingent sequential screening, patients can be classified as high risk, medium risk, or low risk for Down syndrome in the first trimester. Low-risk patients do not return for further screening as their risk of a fetus with Down syndrome is low. When the two types of sequential tests are compared, they have similar overall screen positive rates of 2% to 3%, and both have sensitivities of >90% for trisomy 21 (stepwise, 95%; contingent, 93%)

7. Cell-free fetal DNA screening for aneuploidy. Newer technology has allowed analysis of cell-free fetal

DNA from maternal serum in order to detect trisomies 13, 18, and 21 and sex chromosomal aneuploidies. The fetal DNA detected in maternal serum is placental in origin, can be detected as early as 9 weeks, and can be tested throughout the entire pregnancy. A number of laboratories have commercially available tests; all of which report a high sensitivity and specificity for trisomies 21 and 18. Sensitivity for trisomy 21 is reported at 99.3% and specificity at 99.8%. For trisomy 18, sensitivity is 97.4% and specificity is 99.8%. Sensitivity is lower for trisomy 13 (91%) with a specificity of 99.6%. Importantly, the positive predictive value (PPV) is lower for younger women secondary to the lower prevalence of aneuploidy in this population. For example, for trisomy 21, the PPV is 33% for women <25 years, in comparison to 87% for women >40 years. It is also important to note that cell-free fetal DNA targets specific aneuploidies and will ultimately miss abnormalities in other chromosomes and those with a mosaic karyotype. These abnormalities may have been detected by traditional screening methods. One study estimates up to 17% of significant chromosome abnormalities may go undetected with the use

of cell-free fetal DNA screening alone. For these reasons, cell-free fetal DNA screening for aneuploidy is not recommended for the general obstetric population and currently is recommended for women considered high risk for aneuploidy, including women who are >35 years old, have a history of a fetus or newborn with aneuploidy, carriers of a balanced translocation, or have a positive traditional screening test. Cell-free fetal DNA is considered a screening test, and any positive cell-free fetal DNA result should be followed up with a diagnostic test (CVS or amniocentesis) for confirmation of the diagnosis. Cell-free fetal DNA is also known as noninvasive prenatal testing (NIPT) despite that, as mentioned earlier, this test is considered a screening test and is not diagnostic.

8. Use of ultrasound following serum screening for aneuploidy

a. Second-trimester ultrasound targeted for the detection of aneuploidy has also been successful as a screening tool. Application of secondtrimester ultrasound that is targeted to screen for aneuploidy can decrease the *a priori* maternal age risk of Down syndrome by 50% to 60% as well as the risk conveyed by serum screening. Second-trimester ultrasound following first-trimester screening for aneuploidy has likewise been shown to have value in decreasing the risk assessment for trisomy 21.

B. In women with a **positive family history of genetic disease**, a positive screening test, or at-risk ultrasonographic features, diagnostic tests are considered. When an invasive diagnostic test is performed for a structural abnormality detected on ultrasound, a chromosomal microarray is indicated, which will detect aneuploidy as well as smaller chromosomal deletions and duplications. If an invasive test is performed secondary to a positive screening test, either a chromosomal microarray or a karyotype can be offered. When a significant malformation or a genetic disease is diagnosed prenatally, the information gives the obstetrician and pediatrician time to educate parents, discuss options, and establish an initial neonatal treatment plan before the infant is delivered. In some cases, treatment may be initiated *in utero*.

1. CVS. Under ultrasonic guidance, a sample of placental tissue is obtained through a catheter placed either transcervically or transabdominally. Performed at or after 10 weeks' gestation, CVS provides the earliest possible detection of a genetically abnormal fetus through analysis of trophoblast cells. Transabdominal CVS can also be used as late as the third trimester when amniotic fluid is not available or fetal blood sampling cannot be performed. Technical improvements in ultrasonographic imaging and in the CVS procedure have brought the pregnancy loss rate very close to the loss rate after second-trimester amniocentesis, 0.5% to 1.0%. The possible complications of amniocentesis and CVS are similar. CVS, if performed before 10 weeks of gestation, can be associated with an increased risk of fetal limb-reduction defects and oromandibular malformations.

a. Direct preparations of rapidly dividing cytotrophoblasts can be prepared, making a full karyotype analysis available in 2 days. Although direct preparations minimize maternal cell contamination, most centers also analyze

cultured trophoblast cells, which are embryologically closer to the fetus. This procedure takes an additional 8 to 12 days.

b. In approximately 2% of CVS samples, a mosaic diagnosis is made, which indicates that both karyotypically normal and abnormal cells are identified in the same sample. Because CVS-acquired cells reflect placental constitution, in these cases, amniocentesis is typically performed as a follow-up study to analyze fetal cells. Approximately one-third of CVS mosaicisms are confirmed in the fetus through amniocentesis.

2. Amniocentesis. Amniotic fluid is removed from around the fetus through a needle guided by ultrasonic images. The removed amniotic fluid (˜20 mL) is replaced by the fetus within 24 hours. Amniocentesis can technically be performed as early as 10 to 14 weeks' gestation, although early amniocentesis (<13 weeks) is associated with a pregnancy loss rate of 1% to 2% and an increased incidence of clubfoot. Loss of the pregnancy following an ultrasonography-guided second-trimester amniocentesis (16 to 20 weeks) occurs in 0.5% to 1.0% cases in most centers, so they are usually performed in the second trimester.

a. Amniotic fluid can be analyzed for a number of compounds, including alpha-fetoprotein (AFP), acetylcholinesterase (AChE), bilirubin, and pulmonary surfactant. Increased levels of AFP along with the presence of AChE identify NTDs with >98% sensitivity when the fluid sample is not contaminated by fetal blood. AFP levels are also elevated when the fetus has abdominal wall defects, congenital nephrosis, or intestinal atresias. Several biochemical tests of the amniotic fluid are available to assess fetal lung maturity.

b. Fetal cells can be extracted from the fluid sample and analyzed for chromosomal and genetic makeup.

i. Among second-trimester amniocenteses, 73% of clinically significant karyotype abnormalities relate to one of five chromosomes: 13, 18, 21, X, or Y. These can be rapidly detected using fluorescent *in situ* hybridization (FISH), with sensitivities in the 90% range.

ii. DNA analysis is diagnostic for an increasing number of diseases.

a) Increasingly, **direct DNA methodologies** can be used when the gene sequence producing the disease in question is known. Disorders secondary to deletion of DNA (e.g., α-thalassemia, Duchenne and Becker muscular dystrophy, cystic fibrosis, and growth hormone deficiency) can be detected by the altered size of DNA fragments produced following a polymerase chain reaction (PCR). Direct detection of a DNA mutation can also be accomplished by allele-specific oligonucleotide (ASO) analysis. If the PCR-amplified DNA is not altered in size by a deletion or insertion, recognition of a mutated DNA sequence can occur by hybridization with the known mutant allele. Rapid advances in molecular technologies have provided many new opportunities for mutation identification which are now applicable to fetal DNA.

iii. DNA sequencing for many genetic disorders has revealed that a multitude of different mutations within a gene can result in the same clinical disease. For example, cystic fibrosis can result from >1,000 different mutations. Therefore, for any specific disease, prenatal diagnosis by DNA testing may require parental as well as fetal DNA.

3. Percutaneous umbilical blood sampling (PUBS) is performed under ultrasonic guidance from the second trimester until term. PUBS can provide diagnostic samples for cytogenetic, hematologic, immunologic, or DNA studies; it can also provide access for treatment *in utero*. An anterior placenta facilitates obtaining a sample close to the cord insertion site at the placenta. Fetal sedation is usually not needed. PUBS has a 1% to 2% risk of fetal loss along with complications that can lead to a preterm delivery in another 5%.

4. Preimplantation biopsy or preimplantation genetic diagnosis (PGD). During an *in vitro* fertilization process, early in gestation (at the eightcell stage in humans), prior to transfer, one or two cells can be removed

without known harm to the embryo. PGD is useful for a wide range of autosomal recessive, dominant, and X-linked molecular diagnoses. For couples at risk, testing allows for identification of embryos that carry the disorder in question, and transfer of unaffected embryos can occur. In women who are at risk for X-linked recessive disorders, determination of XX-containing embryos by FISH can enable transfer of only female embryos. Similarly, women at increased risk for a chromosomally abnormal conception can benefit from preimplantation biopsy. When one member of a couple carries a balanced translocation, only those embryos that screen negative for the chromosome abnormality in question are transferred. When more cells are needed for molecular diagnoses, biopsy on day 5 is considered. An alternative approach is analysis of the second polar body, which contains the same genetic material as the ovum. Preimplantation genetic screening (PGS) to assess preimplantation embryos for aneuploidy is not currently considered to provide reproductive advantage to women of advanced maternal age or poor reproductive histories.

5. Cell-free fetal DNA in the maternal circulation. Development of a noninvasive method of prenatal diagnosis for single-gene disorders would be ideal because it would eliminate the potential procedure-related loss of a normal pregnancy. Although fetal cells in the maternal circulation can be separated and analyzed, the limited numbers preclude using this technique on a clinical basis. Cell-free fetal DNA techniques are available commercially for identification of fetal Rh status for women at risk for isoimmunization. Additionally, proof of principle studies have demonstrated this technique for identification of fetuses at risk for single-gene disorders as well but currently are only performed on a research basis.

III. FETAL SIZE AND GROWTH-RATE ABNORMALITIES may have significant implications for perinatal prognosis and care (see Chapter 7). Appropriate fetal assessment is important in establishing a diagnosis and a perinatal treatment plan.

A. Fetal growth restriction (FGR) may be due to conditions in the fetal environment (e.g., chronic deficiencies in oxygen or nutrients or both) or to problems intrinsic to the fetus. It is important to identify constitutionally normal fetuses whose growth is impaired so that appropriate care can begin as soon as possible. Because their risk of mortality is increased severalfold before and during labor, FGR fetuses may need preterm intervention for best survival rates. Once delivered, these newborns are at increased risk for

immediate complications including hypoglycemia and pulmonary hemorrhage, so they should be delivered at an appropriately equipped facility.

Intrinsic causes of FGR include chromosomal abnormalities (such as trisomies, microdeletions, or duplications), congenital malformations, and congenital infections (e.g., cytomegalovirus, toxoplasmosis, varicella, or rubella). Prenatal diagnosis of malformed or infected fetuses is important so that appropriate interventions can be made. Prenatal genetic assessment should be considered if FGR is <3% before 24 weeks or when structural anomalies or soft markers for aneuploidy are present. Investigation by cell-free DNA versus a karyotype/microarray or DNA diagnostic studies is individualized to the specific findings of the case. Prior knowledge that a fetus has a malformation (e.g., anencephaly) or chromosomal abnormality (e.g., trisomy 18) that limits life allows the parents to be counseled before birth of the child and may influence the management of labor and delivery.

1. Definition of FGR. There is no universal agreement on the definition of FGR. Strictly speaking, any fetus that does not reach his or her intrauterine growth potential is included. Typically, fetuses weighing <10th percentile for gestational age are classified as FGR; however, many of these fetuses are normal and at the lower end of the growth spectrum (i.e., “constitutionally small”).

2. Diagnosis of FGR. Maternal clinical exam detects about two-thirds of cases and incorrectly diagnoses it about 50% of the time. Ultrasonography improves the sensitivity and specificity to >80%. FGR may be diagnosed with a single scan when a fetus <10th percentile demonstrates corroborative signs of a compromised intrauterine

environment such as oligohydramnios, an elevated head-abdomen ratio in the absence of central nervous system pathology or abnormal Doppler velocimetry in the umbilical cord. Serial scans documenting absent or poor intrauterine growth regardless of the weight percentile also indicate FGR. From the large Prospective Observational Trial to Optimize Pediatric Health Trial in Intrauterine Growth Restriction (PORTO) study, the greatest risk for morbidity/mortality was among those fetuses below the 3% for estimated fetal weight with abnormal umbilical Doppler perfusion and delayed serial growth trajectory. The use of composite growth profiles derived from a variety of ultrasound measurements and repeated serially to identify individual restriction of fetal growth potential remains controversial.

B. Macrosomia. Macrosomic fetuses (>4,000 g) are at increased risk for shoulder dystocia and traumatic birth injury. Conditions such as maternal diabetes, postterm pregnancy, genetic overgrowth syndromes, and maternal obesity are associated with an increased incidence of macrosomia. Unfortunately, efforts to use a variety of measurements and formulas have met with only modest success in predicting the condition.

IV. FUNCTIONAL MATURITY OF THE LUNGS is one of the most critical variables in determining neonatal survival in the otherwise normal fetus. Currently, however, assessment of fetal maturity is reserved for the infrequent event of semi-elective births before 39 weeks. A number of tests can be performed on amniotic fluid specifically to determine pulmonary maturity (see Chapter 33).

V. ASSESSMENT OF FETAL WELL-BEING. Acute compromise is detected by studies that assess fetal function. Some are used antepartum, whereas others are used to monitor the fetus during labor.

A. Antepartum tests generally rely on biophysical studies, which require a certain degree of fetal neurophysiologic maturity. The following tests are not used until the third trimester; fetuses may not respond appropriately earlier in gestation.

1. Fetal movement monitoring is the simplest method of fetal assessment. Fetuses normally have a sleep-wake cycle, and mothers generally perceive a diurnal variation in fetal activity. Active periods average 30 to 40 minutes. Periods of inactivity >1 hour are unusual in a healthy fetus and should alert the physician to the possibility of fetal compromise. A “count to 10” method by the mother is the only approach to fetal movement which has been validated and then evaluated as a screening test. The same time of day is chosen, fetal movements are noted with the expectation of 10 fetal movements achieved within 2 hours. The average time to 10 movements is 20 minutes (±18). Lack of attaining 10 movements prompts evaluation. However, although a mother's perception of decreased fetal movement should always elicit further surveillance, the specifics of fetal movement quantification remain to be further established.

2. The **nonstress test (NST)** is a reliable means of fetal evaluation. It is simple to perform, relatively quick, and noninvasive, with neither discomfort nor risk to mother or fetus.

The NST is based on the principle that fetal activity results in a reflex acceleration in heart rate. The required fetal maturity is typically reached by approximately 32 weeks of gestation. Absence of these accelerations in a fetus who previously demonstrated them may indicate that hypoxia has sufficiently depressed the central nervous system to inactivate the cardiac reflex. Testing reflexes the current fetal state and cannot predict future events or precisely the neonatal outcome.

The test is performed by monitoring fetal heart rate (FHR) either through a Doppler ultrasonographic device or through skin-surface electrodes on the maternal abdomen. Uterine activity is simultaneously recorded through a tocodynamometer, palpation by trained test personnel, or the patient's report. The test result may be reactive, nonreactive, or inadequate. The criteria for a reactive test are as follows: (i) heart rate between 110 and 160 bpm, (ii) normal beat-to-beat variability (5 bpm), and (iii) two accelerations of at least 15 bpm lasting for not <15 seconds each within a 20-minute period. A nonreactive test is defined as less than two accelerations in 40

minutes. If an adequate fetal heart tracing cannot be obtained for any reason, the test is considered inadequate.

Statistics show that a reactive result is reassuring, with the risk of fetal demise within the week following the test at approximately 3 in 1,000. Negative predictive values for stillbirth within 1 week of reactive NSTs are 99.8%. A nonreactive test is generally repeated later the same day or is followed by another test of fetal well-being. The frequency with which NST should be performed is not established. The NST

is commonly obtained on a weekly basis, although increased testing (two times per week to daily testing) is recommended for high-risk conditions.

3. The **contraction stress test (CST)** may be used as a backup or confirmatory test when the NST is nonreactive or inadequate, although with multiple other modalities for fetal surveillance, CST is now used less commonly.

The CST is based on the idea that uterine contractions can compromise an unhealthy fetus. The pressure generated during contractions can briefly reduce or eliminate perfusion of the intervillous space. A healthy fetoplacental unit has sufficient reserve to tolerate this short reduction in oxygen supply. Under pathologic conditions, however, respiratory reserve may be so compromised that the reduction in oxygen results in fetal hypoxia. Under hypoxic conditions, the FHR slows in a characteristic way relative to the contraction. FHR begins to decelerate 15 to 30 seconds after onset of the contraction, reaches its nadir after the peak of the contraction, and does not return to baseline until after the contraction ends. This heart rate pattern is known as a *late deceleration* because of its relationship to the uterine contraction. Synonyms are type 2 deceleration or deceleration of uteroplacental insufficiency.

Similar to the NST, the CST monitors FHR and uterine contractions. A CST is considered completed if uterine contractions have spontaneously occurred within 30 minutes, lasted 40 to 60 seconds each, and occurred at a frequency of three within a 10-minute interval. If no spontaneous contractions occur, they can be induced with intravenous oxytocin, in which case the test is called an *oxytocin challenge* test.

A CST is positive if late decelerations are consistently seen in association with contractions. A CST is negative if at least three contractions of at least 40 seconds each occur within a 10-minute period without associated late decelerations. A CST is suspicious if there are occasional or inconsistent late decelerations. If contractions occur more frequently than every 2 minutes or last longer than 90 seconds, the study is considered a hyperstimulated test and cannot be interpreted. An unsatisfactory test is one in which contractions cannot be stimulated or a satisfactory FHR tracing cannot be obtained.

A negative CST is even more reassuring than a reactive NST, with the chance of fetal demise within a week of a negative CST being approximately 0.4 per 1,000. If a positive CST follows a nonreactive NST, however, the risk of stillbirth is 88 per 1,000, and the risk of neonatal mortality is also 88 per 1,000. Statistically, about one-third of patients with a positive CST will require cesarean section for persistent late decelerations in labor.

4. The **biophysical profile** combines an NST with other parameters determined by real-time ultrasonic examination. A score of 0 or 2 is assigned for the absence or presence of each of the following: a reactive NST, adequate amniotic fluid volume (vertical fluid pocket >2 cm), fetal breathing movements, fetal activity, and normal fetal musculoskeletal tone. A modified BPP can assess both acute (NST) and chronic stress (amniotic fluid volumes). The total score determines the course

of action. Reassuring tests (8 to 10) are repeated at weekly intervals, whereas less reassuring results (4 to 6) are repeated later the same day. Very low scores (0 to 2) generally prompt delivery. The likelihood that a fetus will die *in utero* within 1 week of a reassuring test is approximately the same as that for a negative CST, which is approximately 0.6 to 0.7 per 1,000. Similarly, the negative predictive value for a stillbirth within 1 week of a

reassuring BPP, modified BPP, and negative CST is >99.9%.

5. Doppler ultrasonography of **fetal umbilical artery blood flow** is a noninvasive technique to assess downstream (placental) resistance. Poorly functioning placentas with extensive vasospasm or infarction have an increased resistance to flow that is particularly noticeable in fetal diastole. Umbilical artery Doppler flow velocimetry is the primary surveillance tool for pregnancies with FGR and utilizes the peak systolic frequency shift (S) and the end-diastolic frequency shift (D). The PORTO study recently established the association of increased morbidity/mortality as occurring primarily among those FGR newborns with abnormal umbilical Doppler studies (pulsatility index >95th percentile or absent/reversed end-diastolic flow). Analyses of placental histology with abnormal umbilical Doppler flow have suggested loss of 70% function is reflected with absent/reversed umbilical Doppler readings. The two commonly used indices of flow are the systolic:diastolic ratio (S/D) and the resistance index (S-D/S). Umbilical artery Doppler velocimetry measurements have been shown to improve perinatal outcome only in pregnancies with a presumptive diagnosis of FGR and should not be used as a screening test in the general obstetric population. The use of umbilical artery Doppler velocimetry measurements, in conjunction with other tests of fetal well-being, can reduce the perinatal mortality in FGR by almost 40%. Doppler measurements of the **middle cerebral artery** can also be used in the assessment of the fetus that is at risk for either FGR or anemia. Further evidence of the progression of uteroplacental insufficiency can be revealed by ultrasound assessment of the ductus venous. Absent or even reversal of the normally forward end-diastolic flow through this vessel is considered a terminal finding. Clinical use remains controversial as the potential benefits of prolonging preterm gestation once abnormal ductus venous flow suggests extreme uteroplacental compromise have not been supported in all studies.

6. Indications for fetal surveillance. Pregnancies with ongoing increased risk for stillbirth (chronic hypertension, pregestational diabetes, poorly controlled gestational diabetes, growth restriction, advanced maternal age, increased maternal body mass, or vascular disease) or new risk (decreased fetal movement, abdominal trauma, vaginal bleeding) are candidates for fetal surveillance. Most fetal surveillance are begun at 32 weeks although in the setting of FGR, in particular, initiation prior to 32 weeks is often undertaken. The frequency of monitoring is typically weekly, although in high-risk conditions or those in which the mother's condition is changing, monitoring will often occur more frequently.

B. Intrapartum assessment of fetal well-being is important in the management of labor.

1. Continuous electronic fetal monitoring is widely used despite the fact that its role in reducing perinatal mortality has been questioned and it does not lower rates of neurologic injury relative to auscultation by trained personnel. It has, however, increased the incidence of operative delivery. When used, the monitors simultaneously record FHR and uterine activity for ongoing evaluation. Either continuous or intermittent monitoring is acceptable for low-risk patients.

a. The **FHR** can be monitored in one of three ways. The noninvasive methods are ultrasonic monitoring and surface-electrode monitoring from the maternal abdomen. The most accurate but invasive method is to place a small electrode into the skin of the fetal presenting part to record the fetal electrocardiogram directly. Placement requires rupture of the fetal membranes. When the electrode is properly placed, it is associated with a very low risk of fetal injury. Approximately 4% of monitored babies develop a mild infection at the electrode site, and most respond to local cleansing.

b. Uterine activity can also be recorded either indirectly or directly. A tocodynamometer can be strapped to the maternal abdomen to record the timing and duration of contractions as well as crude relative intensity. When a more precise evaluation is needed, an intrauterine pressure catheter can be inserted following rupture of the fetal membranes to directly and quantitatively record contraction pressure. Invasive monitoring is associated with

an increased incidence of chorioamnionitis and postpartum maternal infection.

c. Parameters of the fetal monitoring record that are evaluated include the following:

i. Baseline heart rate is normally between 110 and 160 bpm. The baseline must be apparent for a minimum of 2 minutes in any 10-minute segment and does not include episodic changes, periods of marked FHR variability, or segments of baseline that differ by >25 bpm. Baseline fetal bradycardia, defined as an FHR <110 bpm, may result from congenital heart block associated with congenital heart malformation or maternal systemic lupus erythematosus. Baseline tachycardia, defined as an FHR >160 bpm, may result from a maternal fever, infection, stimulant medications or drugs, and hyperthyroidism. Fetal dysrhythmias are typically associated with FHR >200 bpm. In isolation, tachycardia is poorly predictive of fetal hypoxemia or acidosis unless accompanied by reduced beat-to-beat variability or recurrent decelerations.

ii. Beat-to-beat variability is recorded from a calculation of each RR interval. The autonomic nervous system of a healthy, awake term fetus constantly varies the heart rate from beat to beat by approximately 5 to 25 bpm. Reduced beat-to-beat variability may result from depression of the fetal central nervous system due to fetal immaturity, hypoxia, fetal sleep, or specific maternal medications such as narcotics, sedatives, β-blockers, and intravenous magnesium sulfate.

iii. Accelerations of the FHR are reassuring, as they are during an NST.

iv. Decelerations of the FHR may be benign or indicative of fetal compromise depending on their characteristic shape and timing in relation to uterine contractions.

a) Early decelerations are symmetric in shape and closely mirror uterine contractions in time of onset, duration, and termination. They are benign and usually accompany good beat-to-beat variability. These decelerations are more commonly seen in active labor when the fetal head is compressed in the pelvis, resulting in a parasympathetic effect.

b) Late decelerations are visually apparent decreases in the FHR in association with uterine contractions. The onset, nadir, and recovery of the deceleration occur after the beginning, peak, and end of the contraction, respectively. A fall in the heart rate of only 10 to 20 bpm below baseline (even if still within the range of 110 to160 bpm) is significant. Late decelerations are the result of uteroplacental insufficiency and possible fetal hypoxia. As the uteroplacental insufficiency/hypoxia worsens, (i) beat-to-beat variability will be reduced and then lost, (ii) decelerations will last longer, (iii) they will begin sooner following the onset of a contraction, (iv) they will take longer to return to baseline, and (v) the rate to which the fetal heart slows will be lower. Repetitive late decelerations demand action.

c) Variable decelerations vary in their shape and in their timing relative to contractions. Usually, they result from fetal umbilical cord compression. Variable decelerations are a cause for concern if they are severe (down to a rate of 60 bpm or lasting for 60 seconds or longer, or both), associated with poor beatto-beat variability, or mixed with late decelerations. Umbilical cord compression secondary to a low amniotic fluid volume (oligohydramnios) may be alleviated by amnioinfusion of saline into the uterine cavity during labor.

2. National Institute of Child Health and Diseases classification of intrapartum FHR monitoring

a. Endorsed by the American College of Obstetricians and Gynecologists, a three-tiered classification of intrapartum monitoring was introduced in 2008 to promote a systematic interpretation and response to the subjective nature of fetal monitor interpretations. Category I tracings are considered reflexive of a fetus with a normal acid-base status but require repeated review. Category III tracings require prompt intervention, and if unresolved quickly, then delivery. For category II tracings, various precipitating factors may be addressed, and if unsuccessful, then delivery is recommended (see Table 1.1).

3. A **fetal scalp blood sample for blood gas** analysis may be obtained to confirm or dismiss suspicion of fetal hypoxia. An intrapartum scalp pH >7.20 with a base deficit <6 mmol/L is normal. However, these kits are no longer manufactured in the United States. Many obstetric units have replaced fetal scalp blood sampling with noninvasive techniques to assess fetal status. FHR accelerations in response to mechanical

stimulation of the fetal scalp (gently nudging the presenting vertex with the examiner's finger or an Allis clamp) or to vibroacoustic stimulation are reassuring.

Table 1.1. Classification of Intrapartum Monitoring

Category I	Tracings meeting these criteria are predictive of normal fetal acid-base balance at the time of observation.	All of the criteria must be present: ▪ Baseline rate: 110-160 bpm ▪ Moderate baseline FHR variability ▪ No late or variable decelerations ▪ Early decelerations may be present or absent. ▪ Accelerations may be present or absent.
Category II	FHR tracing does not meet criteria for either category I or III and is considered indeterminate.	
Category III	▪ Category III tracings are predictive of abnormal fetal acid-base status at the time of observation. ▪ Prompt evaluation is indicated and intervention indicated.	Either 1 or 2 is present: **1.** Absent baseline FHR variability and any of the following: ▪ Recurrent late decelerations ▪ Recurrent variable decelerations ▪ Bradycardia **2.** Sinusoidal pattern

FHR, fetal heart rate.

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2
Maternal Diabetes Mellitus

Aviva Lee-Parritz

KEY POINTS

- With appropriate management of pregnant women with diabetes, women with good glycemic control and minimal microvascular disease can expect pregnancy outcomes comparable to the general population.
- Women with type 1 and type 2 diabetes are at significantly increased risk for hypertensive disorders, such as preeclampsia, which is potentially deleterious to both maternal and fetal well-being.
- Route of delivery of a fetus affected by maternal diabetes is determined by ultrasonography-estimated fetal weight, maternal and fetal conditions, and previous obstetric history.
- Preconception glucose control for women with pregestational diabetes can reduce the risk of congenital anomalies to near that of the general population.
- Strict glycemic control can reduce fetal macrosomia in both pregestational and gestational diabetes. Targeting postmeal glycemia is more effective than solely premeal measurement to reduce fetal overgrowth.
- Women with pregestational diabetes and microvascular disease are at risk for indicated preterm delivery due to worsening maternal or fetal status.
- Tight intrapartum glucose control is important to reduce fetal oxidative stress and neonatal hypoglycemia.
- Women with pregestational diabetes may have reduced glycemic profiles and insulin requirements postpartum, especially in women breastfeeding.

I. DIABETES AND PREGNANCY OUTCOME. Improved management of diabetes mellitus and advances in obstetrics have reduced the incidence of adverse perinatal outcome in pregnancies complicated by diabetes mellitus. With appropriate management, women with good glycemic control and minimal microvascular disease can expect pregnancy outcomes comparable to the general population. Women with advanced microvascular disease, such as hypertension, nephropathy, and retinopathy, have a 25% risk of preterm delivery because of worsening maternal condition or preeclampsia. Pregnancy does not have a significant impact on the progression of diabetes. In women who begin

pregnancy with microvascular disease, diabetes often worsens, but in most, the disease return to baseline. Preconception glucose control may reduce the rate of complications to as low as that seen in the general population.

II. DIABETES IN PREGNANCY

A. General principles

1. Diabetes that antedates the pregnancy can be associated with adverse fetal and maternal outcomes. The most important complication is diabetic embryopathy resulting in congenital anomalies. Congenital anomalies are associated with 50% of perinatal deaths among women with diabetes compared to 25% among nondiabetic women. The risk of congenital anomalies is related to the glycemic profile at the time of conception. The most common types of anomalies include cardiac malformations and neural tube defects. Women with type 1 and type

2 diabetes are at significantly increased risk for hypertensive disorders, such as preeclampsia, which is potentially deleterious to both maternal and fetal well-being. Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance of variable severity first diagnosed during pregnancy, and it affects 6% to 8% of pregnancies.

2. Epidemiology of gestational diabetes. Approximately 3% to 5% of patients with GDM actually have underlying type 1 or type 2 diabetes, but pregnancy is the first opportunity for testing. Risk factors for GDM include advanced maternal age, multifetal gestation, increased body mass index, and strong family history of diabetes. Certain ethnic groups, such as Native Americans, Southeast Asians, and African Americans, have an increased risk of developing GDM.

3. Physiology unique to women with diabetes antedating pregnancy. In the first half of pregnancy, as a result of nausea and vomiting, **hypoglycemia** can be as much of a problem as **hyperglycemia**. Hypoglycemia, followed by hyperglycemia from counter-regulatory hormones, may complicate glucose control. Maternal hyperglycemia leads to fetal hyperglycemia and fetal hyperinsulinemia, which results in fetal overgrowth. Gastroparesis from long-standing diabetes may be a factor as well. There does not appear to be a direct relationship between hypoglycemia alone and adverse perinatal outcome. Throughout pregnancy, **insulin requirements** increase because of the increasing production of placental hormones that antagonize the action of insulin. This is most prominent in the mid-third trimester and requires intensive blood glucose monitoring and frequent adjustment of medications to control blood glucose.

B. Complications of type 1 and type 2 diabetes during pregnancy

1. Ketoacidosis is an uncommon complication during pregnancy. However, ketoacidosis carries a 50% risk of fetal death, especially if it occurs before the third trimester. Ketoacidosis can be present in the setting of even mild hyperglycemia (200 mg/dL) and should be excluded in every patient with type 1 diabetes who presents with hyperglycemia and symptoms such as nausea, vomiting, or abdominal pain.

2. Stillbirth remains an uncommon complication of diabetes in pregnancy. It is most often associated with poor glycemic control, fetal anomalies, severe vasculopathy, and intrauterine growth restriction (IUGR) as well as severe preeclampsia. Shoulder dystocia that cannot be resolved can also result in fetal death.

3. Polyhydramnios is not an uncommon finding in pregnancies complicated by diabetes. It may be secondary to osmotic diuresis from fetal hyperglycemia. Careful ultrasonographic examination is required to rule out structural anomalies, such as esophageal atresia, as an etiology, when polyhydramnios is present.

4. Severe maternal vasculopathy, especially nephropathy and hypertension, is associated with uteroplacental insufficiency, which can result in IUGR, fetal intolerance of labor, and neonatal complications.

III. MANAGEMENT OF DIABETES DURING PREGNANCY

A. General principles for type 1 or type 2 diabetes. Management of type 1 or type 2 diabetes during pregnancy begins before conception. Tight glucose control is paramount during the periconceptional period and throughout pregnancy. Optimal glucose control requires coordinated care between endocrinologists, maternal-fetal medicine specialists, diabetes nurse educators, and nutritionists. Preconception glycemic control has been shown to decrease the risk of congenital anomalies to close to that of the general population. However, <30% of pregnancies are planned. Physicians should discuss pregnancy planning or recommend contraception for all diabetic women of childbearing age until glycemic control is optimized.

B. General principles for gestational diabetes. In the United States, most women are screened for GDM between 24 and 28 weeks' gestation by a 50-g, 1-hour glucose challenge. A positive result of a blood glucose ≥140 mg/dL is followed by a diagnostic 100-g, 3-hour oral glucose tolerance test (GTT). A positive test is defined

as two or more elevated values on the GTT. There is a current movement to move to a single diagnostic test, consisting of a 75-g, 2-hour GTT, a method that is used uniformly outside of the United States. Uncontrolled pregestational and gestational diabetes can lead to fetal macrosomia and concomitant risk of fetal injury at delivery. GDM shares many features with type 2 diabetes. Women diagnosed with GDM have a 60% lifetime risk of developing overt type 2 diabetes.

1. Testing (first trimester) for type 1 and type 2 diabetes

a. Measurement of glycosylated hemoglobin in the first trimester can give a risk assessment for congenital anomalies by reflecting ambient glucose concentrations during the period of organogenesis.

b. Accurate dating of the pregnancy is obtained by ultrasonography.

c. Ophthalmologic examination is mandatory because retinopathy may progress because of the rapid normalization of glucose concentration in the first trimester. Women with retinopathy need periodic examinations throughout pregnancy, and they are candidates for laser photocoagulation as indicated.

d. Renal function is assessed by either a spot protein/creatinine ratio or spot urine microalbumin, followed by a 24-hour urine collection for protein excretion and creatinine clearance if abnormal. Serum creatinine should also be assessed in patients with long-standing pregestational diabetes. Because the incidence of preeclampsia is significantly elevated in women with diabetes, identification of baseline proteinuria can impact the diagnosis of preeclampsia later in pregnancy.

e. Thyroid function should be evaluated.

f. Nuchal translucency and serum screening for aneuploidy. Although diabetes in and of itself is not a risk factor for aneuploidy, this is part of routine pregnancy care. Nuchal translucency assessment is particularly important because an abnormal measurement is also associated with structural abnormalities, the risk of which is increased in this group of patients.

2. Testing (second trimester) for type 1 and type 2 diabetes

a. Maternal serum screening for neural tube defects is performed between 15 and 19 weeks' gestation. Women with diabetes have a 10-fold increased risk of neural tube defects compared to the general population.

b. All patients undergo a thorough **ultrasonographic survey**, including fetal echocardiography for structural anomalies.

c. Women older than 35 years of age or with other risk factors for fetal aneuploidy are offered **noninvasive prenatal testing or karyotyping via chorionic villus sampling or amniocentesis**.

3. Testing (third trimester) for type 1 and type 2 diabetes, GDM

a. Ultrasonographic examinations are performed monthly through the third trimester for fetal growth measurement.

b. Weekly or twice-weekly fetal surveillance using nonstress testing or biophysical profiles are implemented between 28 and 32 weeks' gestation, depending on glycemic control and other complications.

C. Treatment for all types of glucose intolerance

Strict **diabetic control** is achieved with nutritional modification, exercise and medications, with the traditional goals of fasting glucose concentration <95 mg/dL and postprandial values <140 mg/dL for 1 hour and 120 mg/dL for 2 hours. Recent data have suggested that in pregnant women, euglycemia may be even lower, with fasting glucose levels in the 60 mg/dL range and postmeal glucose levels <105 mg/dL. Insulin therapy has the longest record of accomplishment of perinatal safety. It has been demonstrated that human insulin analogs do not cross

the placenta. More recently, the oral hypoglycemic agents such as glyburide and metformin have been shown to be as effective as insulin in the management of GDM and may be applied to women with pregestational diabetes.

IV. MANAGEMENT OF LABOR AND DELIVERY FOR WOMEN WITH DIABETES

A. General principles. The risk of spontaneous preterm labor is not increased in patients with diabetes, although the risk of iatrogenic preterm delivery is increased for patients with microvascular disease as a result of IUGR, nonreassuring fetal testing, and maternal hypertension. Antenatal corticosteroids for induction of fetal lung maturity (FLM) should be

employed for the usual obstetric indications. Corticosteroids can cause temporary hyperglycemia; therefore, patients may need to be managed with continuous intravenous (IV) insulin infusions until the effect of the steroids wear off. **Delivery is planned** for 39 to 40 weeks, unless other pregnancy complications dictate earlier delivery. Elective delivery after 39 weeks does not require FLM testing. Indicated delivery before 39 weeks' gestation should be carried out without FLM testing. **Route of delivery** is determined by ultrasonography-estimated fetal weight, maternal and fetal conditions, and previous obstetric history. The ultrasonography-estimated weight at which an elective cesarean delivery is recommended is a controversial issue, with the American College of Obstetricians and Gynecologists recommending discussion of cesarean delivery at an estimated fetal weight of >4,500 g due to the increased risk of shoulder dystocia.

B. Treatment. Blood glucose concentration is tightly controlled during labor and delivery. If an induction of labor is planned, patients are instructed to take one-half of their usual basal insulin on the morning of induction. During spontaneous or induced labor, blood glucose concentration is measured every 1 to 2 hours. Blood glucose concentration higher than 120 to 140 mg/dL is treated with an infusion of IV short-acting insulin. IV insulin is very short acting, allowing for quick response to changes in glucose concentration. Active labor may also be associated with hypoglycemia because the contracting uterus uses circulating metabolic fuels. **Continuous fetal monitoring** is mandatory during labor. Cesarean delivery is performed for obstetric indications. The risk of cesarean section for obstetric complications is approximately 50%. Patients with **advanced microvascular disease** are at increased risk for cesarean delivery because of the increased incidence of IUGR, preeclampsia, and nonreassuring fetal status. A history of retinopathy that has been treated in the past is not necessarily an indication for cesarean delivery. Patients with active proliferative retinopathy that is unstable or active hemorrhage may benefit from elective cesarean delivery. **Postpartum**, patients are at increased risk for hypoglycemia, especially in the postoperative setting with minimal oral intake. Patients with pregestational diabetes may also experience a “honeymoon” period immediately after delivery, with greatly reduced insulin requirements that can last up to several days. Lactation is also associated with significant glucose utilization and potential hypoglycemia especially in the immediate postpartum period. For women with type 2 diabetes, the use of metformin and glyburide are compatible with breastfeeding.

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3
Preeclampsia and Related Conditions

Bahaeddine Sibai

Cristina Wallace

KEY POINTS

- Hypertensive disorders in pregnancy are a major cause of maternal morbidity and mortality, accounting for 15% to 20% of maternal deaths worldwide.
- The definitive treatment for preeclampsia is delivery. However, the severity of disease, dilatation/effacement of the maternal cervix, gestational age at diagnosis, and pulmonary maturity of the fetus all influence obstetric management.
- Because of the risks of rapid deterioration, patients with preeclampsia with severe features should be hospitalized after diagnosis at a center with adequate maternal and neonatal resources as well as readily available staff to provide close monitoring and care.
- Elevated blood pressure during pregnancy is associated with an increased risk of developing cardiovascular disease, chronic kidney disease, and diabetes mellitus later in life.

I. CATEGORIES OF PREGNANCY-ASSOCIATED HYPERTENSIVE DISORDERS

A. Chronic hypertension. Hypertension preceding pregnancy or first diagnosed before 20 weeks' gestation

B. Chronic hypertension with superimposed preeclampsia. Worsening hypertension and new-onset proteinuria, in addition to possible concurrent thrombocytopenia, or transaminase derangements after the 20th week of pregnancy in a woman with known chronic hypertension. It can be further subdivided into with or without severe features.

C. Gestational hypertension. Hypertension without proteinuria and without symptoms or abnormal laboratory tests after 20 weeks' gestation (Table 3.1)

D. Preeclampsia. Blood pressures >140 mm Hg systolic or 90 mm Hg diastolic with proteinuria after 20 weeks' gestation. It can be further subdivided into with or without severe features.

E. Eclampsia. Generalized tonic-clonic seizure activity in a pregnant woman with no prior history of a seizure disorder

F. Hemolysis, elevated liver enzymes, and low platelets syndrome. Clinical findings consistent with hemolysis, elevated liver function tests, and thrombocytopenia

Table 3.1. Diagnosis of Preeclampsia versus Gestational Hypertension

Recommendation	Gestational Hypertension	Preeclampsia

HTN >20 weeks	Yes	Yes
Previously normotensive	Yes	Yes
SBP: 140-159 mm Hg	Yes	Yes
DBP: 90-109 mm Hg	Yes	Yes
Persistent for 4 hours	Yes	Yes
Presence of symptoms	No	No
Normal blood tests	Yes	Yes
Proteinuria: ≥300 mg/24 hours Protein/creatinine ratio ≥0.3 Urine dip stick ≥1 +	No	Yes

HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure.

II. INCIDENCE AND EPIDEMIOLOGY. Hypertensive disorders in pregnancy are a major cause of maternal morbidity and mortality, accounting for 15% to 20% of maternal deaths worldwide. In the United States, hypertensive disorders are the second leading cause of maternal mortality after thrombotic/hemorrhagic complications. Beyond 20 weeks' gestation, preeclampsia complicates 5% to 8% of pregnancies, and preeclampsia with severe features complicates <1% of pregnancies. Eclampsia itself is much less frequent, occurring in 0.1% of pregnancies. Several risk factors have been identified, as outlined in Table 3.2.

Preeclampsia has been called the “disease of theories,” and many **etiologies** have been proposed. What is clear, however, is that it is a condition of dysfunction within the maternal endothelium. Increased levels of the soluble receptors *sFLT1* and *endoglin* within the maternal circulation for vascular endothelial growth factor (VEGF) and transforming growth factor-β (TGF-β), respectively, may be associated with preeclamptic pathology. Higher circulating levels of these soluble receptors reduce the bioavailable levels of VEGF, placental growth factor (PlGF), and TGF-β, resulting in endothelial dysfunction within the maternal circulatory system. This dysfunction can manifest as both increased arterial tone (hypertension) and increased capillary leak (edema/proteinuria/pulmonary congestion). It is unclear what insult prompts the initial increase in sFLT1 and endoglin in some women versus others. One suggestion has been that abnormal trophoblastic invasion of both the maternal decidual arteries with an accompanying abnormal maternal immune response is at the root of this condition. This abnormal placentation is believed to lead to a reduction in placental perfusion and relative placental ischemia. Both sFLT1 and endoglin are proangiogenic proteins and may represent a placental

compensatory response. Recent work has, however, called the implied causality of this hypothesis into question; in early pregnancy, when placental formation is most active, sFLT1 and P1GF levels have failed to reliably predict the occurrence of preeclampsia.

Table 3.2. Risk Factors for Hypertensive Disorders

Risk Factors

Nulliparity

Age >40 years

Obesity

Preeclampsia in previous pregnancy

Family history of preeclampsia

Preexisting chronic hypertension

Chronic renal disease

History of thrombophilia

Diabetes (type 1 or type 2)

Multifetal pregnancy

Systemic lupus erythematosus

In vitro fertilization

Molar pregnancy

Fetal hydrops

Source: From the American College of Obstetricians and Gynecologists. Hypertension in pregnancy. http://www.acog.org/Resources-And-Publications/Task-Force-and-Work-Group-Reports/Hypertension-in-Pregnancy. Accessed May 28, 2016; and Moussa H, Arian S, Sibai B. Management of hypertensive disorders in pregnancy. *Womens Health (Lond Engl)* 2014;10(4):385-404.

III. DIAGNOSIS. The classic presentation which defines preeclampsia is hypertension and proteinuria after 20 weeks' gestation. Some patients will also have nondependent edema, but this is no longer a part of the diagnostic criteria for preeclampsia. The clinical spectrum of preeclampsia ranges from mild to severe. Most patients have a nonsevere form of the disease that develops late in the third trimester (Fig. 3.1).

A. Criteria for the diagnosis of preeclampsia without severe features

1. Hypertension defined as a blood pressure elevation to 140 mm Hg systolic or 90 mm Hg diastolic over two measurements at least 4 hours apart.

Measurements should be taken in the sitting position at the level of the heart, and the proper cuff size needs to

be ensured.

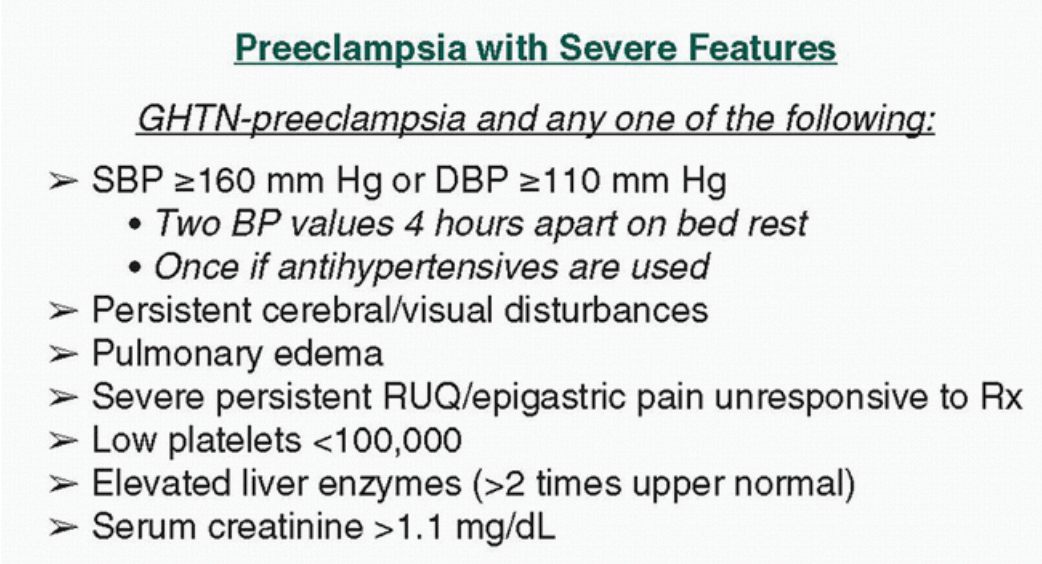

Figure 3.1. Diagnosis of preeclampsia with severe features. GHTN, gestational hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; RUQ, right upper quadrant; Rx, reaction.

2. Proteinuria defined as at least 300 mg of protein in a 24-hour period or protein to creatinine ratio ≥0.3 mg/mg.

B. Criteria for the diagnosis of preeclampsia with severe features *Of note, you do not need every criteria listed here to make a diagnosis.*

1. Blood pressure >160 mm Hg systolic or 110 mm Hg diastolic with the diagnostic readings taken twice at least 4 hours apart or severe hypertension can be verified within minutes to aid in administering antihypertensive therapy.

2. Symptoms suggestive of end-organ dysfunction. New visual disturbances such as scotomata, diplopia, blindness, or persistent severe headache. Other symptoms such as severe persistent right upper quadrant pain or severe epigastric pain not responsive to medications and not attributed to another medical cause are suggestive of preeclampsia with severe features.

3. Pulmonary edema

4. Renal insufficiency is defined as serum creatinine >1.1 mg/dL.

5. Thrombocytopenia is defined as a platelet count of <100,000.

6. Hepatocellular dysfunction. Elevated transaminases (to twice upper limit of normal concentration)

C. HELLP syndrome stands for hemolysis, elevated liver enzymes, and low platelets. It represents an alternative presentation of preeclampsia and reflects systemic end-organ damage. HELLP syndrome may appear without either hypertension or proteinuria.

IV. COMPLICATIONS. Complications of preeclampsia result in a maternal mortality rate of 3 per 100,000 live births in the United States. Maternal

morbidity may include central nervous system complications (e.g., seizures, intracerebral hemorrhage, and blindness), disseminated intravascular coagulation (DIC), hepatic failure or rupture, pulmonary edema, and *abruptio placentae* leading to maternal hemorrhage and/or acute renal failure. Fetal mortality markedly increases severity of disease process. Fetal morbidity may include intrauterine fetal growth restriction, fetal acidemia, and complications from prematurity.

V. CONSIDERATIONS IN MANAGEMENT

A. The definitive treatment for preeclampsia is delivery. However, the severity of disease, dilatation/effacement of the maternal cervix, gestational age at diagnosis, and pulmonary maturity of the fetus all influence obstetric management. Delivery is usually indicated if there is nonreassuring fetal testing in a viable fetus or if the maternal status becomes unstable regardless of either gestational age or fetal maturity.

B. Delivery should be considered for all patients at ≥37 weeks with any degree of gestational hypertension or preeclampsia.

C. Pregnancies may continue for patients with **preterm gestation and preeclampsia without severe features/gestational hypertension**, with close observation as outlined in section VI until 37 weeks' gestation or some other ominous development such as the progression to preeclampsia with severe features, nonreassuring fetal testing, or maternal instability.

D. If the patient has preeclampsia with severe features, treatment varies based on the severity of the patient's disease and the gestational age. If the patient is >34 weeks, the recommendation by the American College of Obstetricians and Gynecologists (ACOG) is delivery. Prior to 34 weeks, three management options include delivery immediately, betamethasone then delivery, and expectant management. The timing of delivery is discussed in further detail in section VII.

E. Expectant management entails hospitalization and frequent maternal and fetal surveillance. This should only be undertaken in carefully selected patients after an initial period of observation to ensure stability of the pregnant woman. Monitoring of these patients includes daily maternal-fetal testing, routine vital signs, and monitoring for symptoms of preeclampsia. Patients may even be given oral antihypertensive drugs to bring their blood pressure down. Women with uncontrolled hypertension despite maximum doses of antihypertensive medications, thrombocytopenia, hepatocellular dysfunction, pulmonary edema, compromised renal function, or persistent headache or visual changes are not candidates for expectant management.

F. The mode of delivery does not need to be a cesarean section. A number of factors have to be assessed including the fetal position, maternal status, gestational age, cervical status, and fetal condition. At earlier gestational ages, a trial of labor induction is not contraindicated in patients with preeclampsia with severe features; however, the success rate is low. The managing team must balance the risks of progression of the disease against the time required to induce labor.

VI. CLINICAL MANAGEMENT OF PREECLAMPSIA WITHOUT SEVERE FEATURES

A. Antepartum management. Conservative management of preeclampsia without severe features generally consists of daily assessment by the maternal symptoms and fetal movement by the women, biweekly blood pressure checks, and weekly assessment of platelet counts and liver enzymes. It is recommended that strict bed rest and salt restriction not be prescribed in these women.

1. Fetal evaluation

a. An initial ultrasound should be performed at the time of diagnosis to rule out intrauterine fetal growth restriction and/or oligohydramnios. A nonstress test (NST) or biophysical profile may also be performed as indicated.

b. Ultrasonography every 3 weeks for growth is recommended. Twiceweekly NSTs with amniotic fluid index measurements are recommended. The frequency of these tests can be changed based on the findings noted during the evaluations.

c. Any **change in maternal status** should prompt evaluation of fetal status.

d. Fetal indications for delivery include nonreassuring fetal testing. If severe growth restriction and/or

oligohydramnios is noted, then further assessment of the fetus is recommended with umbilical artery Doppler studies.

2. Maternal evaluation

a. Women should be **evaluated for signs and symptoms** of preeclampsia with severe features.

b. Initial laboratory evaluation includes platelet count, transaminases, hemoglobin/hematocrit, creatinine, and urine protein-to-creatinine ratio.

c. If criteria for preeclampsia with severe features are not met, laboratory studies should be performed at weekly intervals to assess for worsening disease.

d. Maternal indications for delivery include a gestational age ≥37 weeks; thrombocytopenia (<100,000); progressive deterioration in hepatic or renal function; placental abruption; and persistent severe headaches, visual changes, or epigastric pain.

e. Antihypertensive agents are not routinely given because they have not been shown to improve the outcome in cases of preeclampsia without severe features.

f. When early delivery is indicated, it is our practice that vaginal delivery is preferred. Cesarean delivery should be reserved for cases with nonreassuring fetal testing, when further fetal evaluation is not possible, or when a rapidly deteriorating maternal condition mandates expeditious delivery (e.g., HELLP syndrome with decreasing platelet counts, abruption).

B. Intrapartum management of preeclampsia

1. Magnesium sulfate is not routinely recommended for women with preeclampsia without severe features or gestational hypertension unless

symptoms of worsening disease are noted such as systolic blood pressure >160 mm Hg, diastolic blood pressure >110 mm Hg, or maternal symptoms noted.

2. Antihypertensive therapy is not recommended unless the systolic blood pressure is >160 mm Hg or the diastolic blood pressure is >110 mm Hg.

3. Continuous electronic fetal monitoring is recommended given the potential for placental dysfunction in the preeclamptic setting. Monitoring should be established during the initial evaluation, induction of labor, and labor itself. Continuous monitoring is not recommended during intervals of prolonged expectant management. Patterns that suggest fetal compromise include persistent tachycardia, minimal or absent fetal heart rate variability, and recurrent variable or late decelerations not responsive to standard resuscitative measures.

4. Patients may be safely administered **epidural anesthesia** if the platelet count is >70,000 and there is no evidence of DIC. Consideration should be given for early epidural catheter placement when the platelet count is reasonable and there is concern that it is decreasing. Any anesthesia should be administered by properly trained personnel experienced in the care of women with preeclampsia given the hemodynamic changes associated with the condition. Adequate preload should be ensured to minimize the risk of hypotension.

5. Invasive central monitoring of the mother is rarely indicated, even in the setting of preeclampsia with severe features.

C. Postpartum management. The mother's condition may worsen immediately after delivery. However, signs and symptoms usually begin to resolve within 24 to 48 hours postpartum, and in most women, it usually resolves within 1 or 2 weeks.

VII. MANAGEMENT OF PREECLAMPSIA WITH SEVERE FEATURES (Fig. 3.2)

A. Timing of delivery

1. If <23 weeks' or >**34 weeks' gestation**, delivery is indicated.

2. Prior to 34 weeks, **expectant management** can be attempted unless there is evidence of eclampsia, pulmonary edema, DIC, uncontrollable severe hypertension, nonviable fetus, abnormal fetal test results, placental abruption, or intrapartum fetal demise. In those situations, the goal is to stabilize the mother and then deliver. If the patient has evidence of persistent symptoms, HELLP, partial HELLP, fetal growth restriction with severe oligohydramnios (largest vertical pocket <2 cm) or reversed end-diastolic flow on umbilical artery Doppler studies, labor, or significant renal dysfunction, the goal is to administer betamethasone for fetal lung maturity and plan on delivery after 48 hours. If the patient does not meet any of the criteria for delivery, expectant management is recommended until 34 weeks or delivery can be performed sooner if the patient develops evidence of worsening disease. Two randomized trials performed in the United States compared immediate delivery

versus expectant management in mothers with preeclampsia with severe features. These trials showed that expectant management led to prolongation of pregnancy by about 7 days with a significant reduction in total neonatal complications from 75% to 33%. The disadvantage of expectant management is that preeclampsia with severe features can lead to acute and long-term complications for the patient including the progressive deterioration of the maternal and fetal condition.

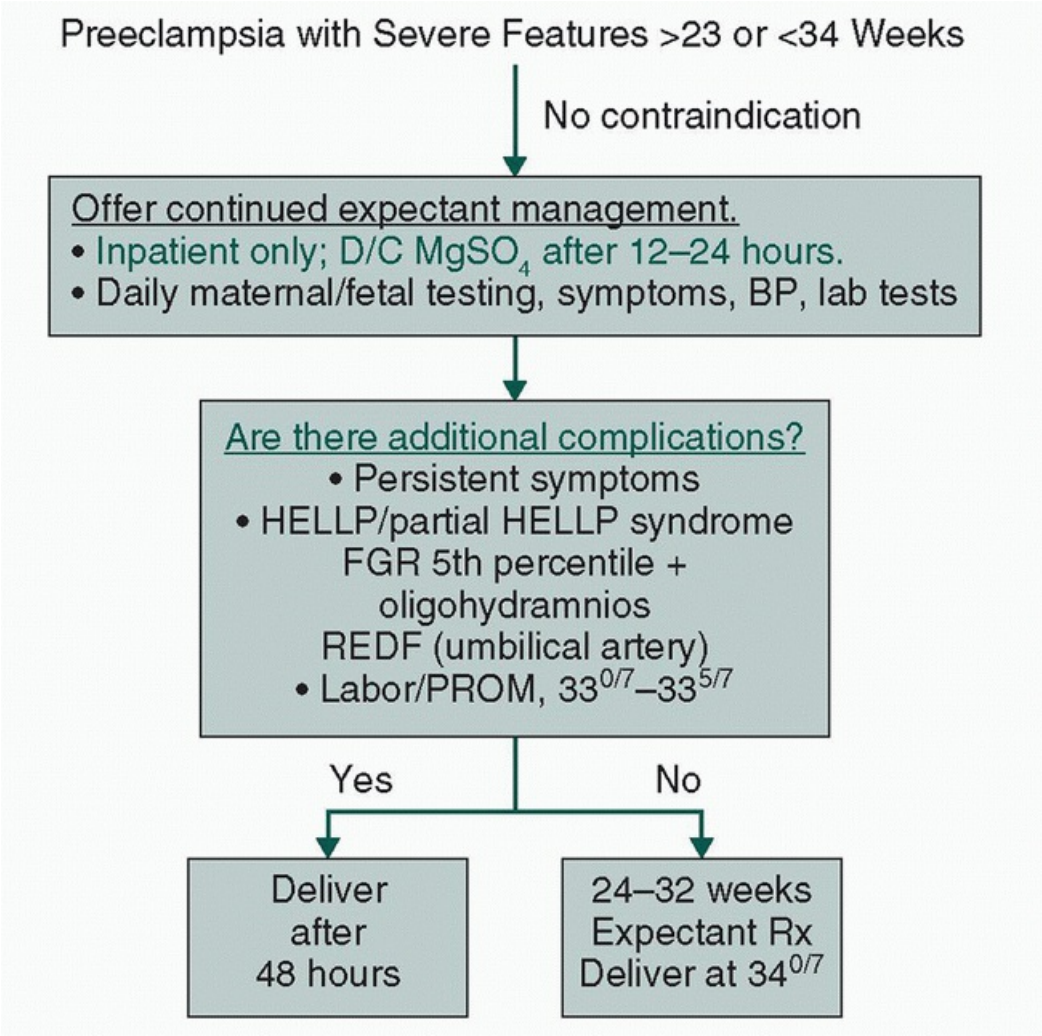

Figure 3.2. Management of preterm preeclampsia with severe features. D/C, discontinue; $MgSO_4$, magnesium sulfate; BP, blood pressure; HELLP, hemolysis, elevated liver enzymes, and low platelets; FGR, fetal growth restriction; REDF, reversed end diastolic flow; PROM, premature rupture of membrane; Rx, reaction.

3. Because of the risks of rapid deterioration, patients with preeclampsia with severe features should be hospitalized after diagnosis at a center with adequate maternal and neonatal resources as well as readily available staff to provide close monitoring and care.

B. Intrapartum management

1. Magnesium sulfate (6 g intravenous [IV] load followed by 2 g/hour infusion) is used as seizure prophylaxis. It is started when the decision to proceed with delivery is made and is continued for at least 24 hours postpartum. Magnesium sulfate has been shown to be the agent of choice for seizure prophylaxis in randomized double-blind comparisons against both placebo and conventional antiepileptics. In patients with myasthenia gravis or hypocalcemia, magnesium sulfate

is contraindicated and should not be given. Because magnesium sulfate is excreted from the kidneys, urine output should be carefully monitored. Signs and symptoms of maternal toxicity include loss of deep tendon reflexes, somnolence, respiratory depression, cardiac arrhythmia, and in extreme cases, cardiovascular collapse.

2. Careful monitoring of fluid balance is critical because preeclampsia is associated with endothelial dysfunction leading to decreased intravascular volume, pulmonary edema, and oliguria. A serum magnesium level should be considered if reduced renal function is suspected while magnesium sulfate is being administered. In addition, if the patient has evidence of reduced kidney function, that is, serum creatinine >1.1 mg/dL, magnesium sulfate maintenance dose can be started at 1 g/hour after the initial bolus. If the patient's creatinine is >2.5 mg/dL, a maintenance dose may not be necessary.

3. Continuous fetal heart rate monitoring is recommended. Reduced fetal heart rate variability may also result from maternal administration of magnesium sulfate.

4. Severe hypertension may be controlled with agents including IV hydralazine, IV labetalol, or oral nifedipine. Sodium nitroprusside should be avoided before delivery because of potential fetal cyanide toxicity. It is important to avoid large or abrupt reductions in blood pressure because decreased intravascular volume and poor uteroplacental perfusion can lead to acute placental insufficiency and a resulting loss of reassurance regarding fetal well-being.

C. Postpartum management

1. Because postpartum eclamptic seizures generally occur within the first 48 hours and usually within the first 24 hours after delivery, magnesium sulfate prophylaxis is continued for at least 24 hours. Close monitoring of fluid balance is continued. While on magnesium sulfate, the patient's blood pressure is monitored closely, urine output, lung evaluation, and deep tendon reflexes for evidence of magnesium sulfate toxicity.

2. Hypertension >150 mm Hg systolic or 100 mg Hg diastolic on at least two occasions 4 to 6 hours apart needs to be treated in the postpartum period with antihypertensive therapy. Some patients, although sufficiently stable for discharge, may require antihypertensive medications for up to 8 weeks after delivery.

3. Typically, blood pressures tend to decrease within the first 48 hours after delivery and increase 3 to 6 days later. It is recommended to monitor patients' blood pressures closely for 72 hours after delivery, preferably in the hospital, and then to have the patient return to clinic 7 to 10 days after delivery again to reassess blood pressure. If the patient develops symptoms of preeclampsia in the interim, he or she should be assessed again sooner.

4. Nonsteroidal anti-inflammatory agents generally should be avoided in the postpartum period in patients with severe hypertension and in those with superimposed preeclampsia. These medications can increase blood pressure and increase sodium retention.

VIII. MANAGEMENT OF ECLAMPSIA

A. Approximately half of **eclamptic seizures** occur before delivery, 20% occur during delivery, and another 30% occur in the postpartum period. Although there is no clear constellation of symptoms that will accurately predict which patients will have an eclamptic seizure, headache is a frequently reported heralding symptom, but most preeclamptic women with headaches do not develop seizures.

B. Basic principles of maternal resuscitation should be followed in the initial management of an eclamptic seizure: airway protection, oxygen supplementation, left lateral displacement to prevent uterine compression of vena cava, intravenous access, and blood pressure control.

C. Magnesium sulfate should be initiated for **prevention of recurrent seizures**. Ten percent of women with eclamptic seizures will have a recurrent seizure after initiation of magnesium sulfate.

D. A **transient fetal bradycardia** is usually seen during the seizure followed by a **transient fetal tachycardia** with loss of variability. Ideally, the fetus should be resuscitated *in utero*.

E. Eclampsia is an indication for delivery but not necessarily an indication for cesarean delivery. No intervention should be initiated until maternal stability is ensured and the seizure is over. Because of the risk of DIC, coagulation parameters should be assessed and appropriate blood products should be available if necessary.

F. A **neurologic exam** should be performed once the patient recovers from the seizure. If the seizure is atypical or any neurologic deficit persists, **brain imaging** is indicated.

G. If a patient has recurrent seizures while on magnesium sulfate, a reloading dose of 2 g of magnesium sulfate can be given one or two times. If seizures persist after two additional boluses of magnesium sulfate, consideration should be given to adding IV lorazepam.

IX. RECURRENCE RISK. Patients who have a history of preeclampsia are at increased risk for hypertensive disease in a subsequent pregnancy. Recurrence risk is as high as 40% in women with preeclampsia before 32 weeks of gestation, as opposed to 10% or less in women with preeclampsia near term. Severe disease and eclampsia are also associated with recurrence. Racial differences exist, with African American women having higher recurrence rates. The recurrence rate for HELLP syndrome is approximately 5%.

X. RISK OF CHRONIC HYPERTENSION. Elevated blood pressure during pregnancy, regardless of type and even without known risk factors, can be indicative of a high risk of cardiovascular disease, chronic kidney disease, and diabetes mellitus later in life. In addition, women with recurrent preeclampsia, women with early-onset preeclampsia, and multiparas with a diagnosis of preeclampsia (even if not recurrent) may be at an even higher risk than those with just gestational hypertension. Given this high risk of future morbidity, the ACOG Task Force on Hypertension in Pregnancy recommends that women with a

history of preeclampsia delivered prior to 37 weeks or who have had recurrent preeclampsia be screened annually for blood pressure, lipids, fasting blood glucose, and body mass index.

XI. INNOVATIONS AND PROPOSED TREATMENTS

A. Several analytic assays based on sFLT1 and PlGF protein levels and soluble endoglin early in the second trimester are currently under evaluation. The ultimate clinical utility of these analytes has yet to be determined. Some newer studies show that these biomarkers in combination with uterine artery Dopplers may be predictive of early-onset preeclampsia. In addition, randomized trials are ongoing to evaluate several modalities to prolong gestation during expectant management of early onset preeclampsia.

B. Low-dose aspirin is recommended for women with a medical history of preeclampsia <34 weeks or preeclampsia in more than one previous pregnancy. The recommended dose is between 60 and 80 mg, and it should be started late in the first trimester.

C. Although earlier studies suggested that **antenatal calcium supplementation** may reduce the incidence of hypertensive disorders of pregnancy, a large National Institutes of Health-sponsored placebo-controlled trial did not show any benefit when given to healthy nulliparous women. This is especially true in populations like the United States where calcium intake is adequate.

D. Recent enthusiasm for antioxidant therapy has also been dulled after a wellexecuted trial found vitamin E supplementation during pregnancy to be associated with an increased risk of adverse outcome compared with placebo.

XII. IMPLICATIONS FOR THE NEWBORN

A. Infants born to mothers with preeclampsia with severe features or superimposed preeclampsia may show evidence of **IUGR** and are frequently delivered prematurely. They may tolerate labor poorly and therefore require resuscitation.

B. Medications used ante- or intrapartum may affect the fetus.

1. Short-term sequelae of hypermagnesemia, such as hypotonia and respiratory depression, are sometimes seen. Long-term maternal administration of magnesium sulfate has rarely been associated with neonatal parathyroid abnormalities or other abnormalities of calcium homeostasis

2. Antihypertensive medications, including calcium channel blockers, may have fetal effects, including hypotension in the infant. Antihypertensive medications and magnesium sulfate generally are not contraindications to breastfeeding.

3. Low-dose aspirin therapy does not appear to increase the incidence of intracranial hemorrhage, asymptomatic bruising, bleeding from circumcision sites, or persistent pulmonary hypertension.

4. Approximately one-third of infants born to mothers with early-onset preeclampsia with severe features have **decreased platelet counts at birth**, but the counts generally increase rapidly to normal levels. Approximately 40% to 50% of newborns have neutropenia that generally resolves before 3 days of age. These infants may be at increased risk for neonatal infection.

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4
Resuscitation in the Delivery Room

Steven A. Ringer

KEY POINTS

- Anticipation is key to ensuring that adequate preparations have been made for a neonate likely to require resuscitation at birth.
- The primary goal in neonatal resuscitation must be to ensure an adequate airway and respiration
- Thermal control should be of paramount concern and additional steps taken to ensure that the infant temperature remains normal during transition.

I. GENERAL PRINCIPLES. A person skilled in basic neonatal resuscitation, whose primary responsibility is the newly born baby, should be present at every birth. Delivery of all high-risk infants should be ideally attended by personnel who possess the skills required to perform a complete resuscitation.

The highest standard of care requires the following: (i) knowledge of perinatal physiology and principles of resuscitation, (ii) mastery of the technical skills required, and (iii) a clear understanding of the roles of other team members and coordination among team members. This allows anticipation of each person's reactions in a specific instance and helps ensure that care is timely and comprehensive. Completion of the Newborn Resuscitation Program (NRP) of the American Academy of Pediatrics/American Heart Association by every caregiver helps ensure a consistent approach to resuscitations and team-based training. NRP provides an approach to resuscitation that is successful in a very high percentage of cases and aids clinicians in more rapidly identifying those unusual cases in which specialized interventions may be required.

A. Perinatal physiology. Resuscitation efforts at delivery are designed to help the newborn make the respiratory and circulatory transitions that must be accomplished immediately after birth: The lungs expand, fetal lung fluid is cleared, effective air exchange is established, and the right-to-left circulatory shunts terminate. The critical period for these physiologic changes is during the first several breaths, which result in lung expansion and elevation of the partial pressure of oxygen (PO_2) in both the alveoli and the arterial circulation. Elevation of the PO_2 from the fetal level of approximately 25 mm Hg to values of 50 to 70 mm Hg is associated with (i) decrease in pulmonary vascular resistance, (ii) decrease in right-to-left shunting through the ductus arteriosus, (iii) increase in venous return to

the left atrium, (iv) rise in left atrial pressure, and (v) cessation of right-toleft shunt through the foramen ovale. The end result is conversion from fetal to transitional to neonatal circulatory pattern. Adequate systemic arterial oxygenation results from perfusion of well-expanded, well-ventilated lungs and adequate circulation.

Conditions at delivery may compromise the fetus's ability to make the necessary transitions. Alterations in tissue perfusion and oxygenation ultimately result in depression of cardiac function, but human fetuses initially respond to hypoxia by becoming apneic. Even a relatively brief period of oxygen deprivation may result in this **primary apnea**. Rapid recovery from this state is generally accomplished with appropriate stimulation and oxygen exposure. If the period of hypoxia continues, the fetus will irregularly gasp and lapse into **secondary apnea**. This state may occur remote from birth or in the peripartum period. Infants born during this period require

resuscitation with assisted ventilation and oxygen (see section III.B).

B. Timing of cord clamping. The following discussion focuses on infants who require some measure of resuscitation after birth. For the majority of infants, no additional steps are needed beyond drying and provision of warmth and initial stimulation. If the infant is breathing spontaneously at birth, the cord should not be clamped and divided until at least 30 to 60 seconds have passed. The infant should be placed on the maternal chest or abdomen, be dried, and kept warm.

For those infants who require resuscitation beyond the initial steps because of inadequate or absent respiratory effort, the cord should be clamped and divided shortly after birth. Ongoing studies continue to evaluate the feasibility and effectiveness of providing resuscitation with the umbilical circulation still intact.

C. Goals of resuscitation are the following:

1. Minimizing immediate heat loss by drying and providing warmth, thereby decreasing oxygen consumption by the neonate

2. Establishing normal respiration and lung expansion by clearing the upper airway and using positive-pressure ventilation if necessary

3. Increasing arterial PO_2 by providing adequate alveolar ventilation. The **routine** use of added oxygen is not warranted, but this therapy may be necessary in some situations.

4. Supporting adequate cardiac output

II. PREPARATION. Anticipation is key to ensuring that adequate preparations have been made for a neonate likely to require resuscitation at birth. It is estimated that as many as 10% of neonates require some assistance at birth for normal transition, whereas <1% require extensive resuscitative measures.

A. Perinatal conditions associated with high-risk deliveries. Ideally, the obstetrician should notify the pediatrician well in advance of the actual birth. The pediatrician may then review the obstetric history and events leading to the high-risk delivery and prepare for the specific problems that may be anticipated. If time permits, the problems should be discussed with

the parent(s). The following antepartum and intrapartum events warrant the presence of a resuscitation team at delivery.

1. Evidence of nonreassuring fetal status

a. Category III fetal tracing including either sinusoidal pattern or absent fetal heart rate (FHR) variability and any of the following: late decelerations, recurrent variable decelerations, or bradycardia

b. History of an acute perinatal event (e.g., placental abruption, cord prolapse or abnormal fetal testing, or a scalp pH of 7.20 or less)

c. History of decreased fetal movement, diminution in growth, or abnormalities of umbilical vessel Doppler flow studies

2. Evidence of fetal disease or potentially serious conditions (see Chapter 1 **)**

a. Meconium staining of the amniotic fluid and/or other evidence of possible fetal compromise (see Chapter 35)

b. Prematurity (<37 weeks), postmaturity (>42 weeks), anticipated low birth weight (<2.0 kg), or high birth weight (>4.5 kg)

c. Major congenital anomalies diagnosed prenatally

d. Hydrops fetalis

e. Multiple gestation (see Chapter 11)

3. Labor and delivery conditions

a. Significant vaginal bleeding

b. Abnormal fetal presentation

c. Prolonged or unusual labor

d. Concern about a possible shoulder dystocia

B. The following conditions do not require a pediatric team to be present, but personnel should be available for assessment and triage.

1. Neonatal conditions

a. Unexpected congenital anomalies

b. Respiratory distress

c. Unanticipated neonatal depression, for example, Apgar score of <6 at 5 minutes

2. Maternal conditions

a. Signs of maternal infection

i. Maternal fever

ii. Membranes ruptured for >24 hours

iii. Foul-smelling amniotic fluid

iv. History of sexually transmitted disease

b. Maternal illness or other conditions

i. Diabetes mellitus

ii. Rh or other isoimmunization without evidence of hydrops fetalis

iii. Chronic hypertension or pregnancy-induced hypertension

iv. Renal, endocrine, pulmonary, or cardiac disease

v. Alcohol or other substance abuse

c. Mode of delivery

In the absence of other antenatal risk factors, delivery via cesarean section done using regional anesthesia at >37 to 39 weeks' gestation does not increase the likelihood of a baby requiring endotracheal (ET) intubation, compared to vaginal delivery at term.

C. Necessary equipment must be present and operating properly. Each delivery room should be equipped with the following:

1. Radiant warmer with procedure table or bed. The warmer should be turned on and checked before delivery. For a very low birth weight (VLBW) infant, additional warming techniques should be available, which might include prewarming the delivery room to 26°C, plastic wrap for covering the baby, or the use of an exothermic mattress. When used in combination, care should be taken to avoid hyperthermia.

2. A blended oxygen source (adjustable between 21% and 100%) with adjustable flowmeter and adequate length of tubing. A humidifier and heater may be desirable.

3. Pulse oximeter available for use when oxygen therapy is anticipated.

4. Flow-inflating **bag** with adjustable pop-off valve or self-inflating bag with reservoir. The bag must be appropriately sized for neonates (generally about 750 mL) and capable of delivering 100% oxygen.

5. Face mask(s) of appropriate size for the anticipated infant

6. A bulb syringe for suctioning

7. Stethoscope with infant- or premature-sized head

8. Equipped emergency box or cart

a. Laryngoscope with no. 0 and no. 1 blades. For extremely low birth weight infants, a no. 00 blade may be preferred.

b. Extra batteries

c. Uniform diameter ET tubes (2.5-, 3.0-, and 3.5-mm internal diameters), two of each

d. Drugs, including epinephrine (1:10,000), and NaCl 0.9% (normal saline). Sodium bicarbonate (0.50 mEq/mL) and naloxone are rarely useful and are not part of usual resuscitation algorithm.

e. Umbilical catheterization tray with 3.5 and 5 French catheters

f. Syringes (1.0, 3.0, 5.0, 10.0, and 20.0 mL), needles (18 to 25G), T-connectors, and stopcocks

9. Transport incubator with battery-operated heat source and portableblended oxygen supply should be available if delivery room is not close to the nursery.

10. Pulse oximetry is recommended when oxygen is being administered and/or positive-pressure ventilation is used more than for a few breaths. It can be applied immediately after birth and successfully used to provide information on oxygen saturation and heart rate. It may take around 60 to 90 seconds to obtain an accurate reading; pulse oximetry may fail if cardiac output is low.

11. Electrocardiography can be used if there is a question about the heart rate. Leads can be quickly applied and the heart rate determined within about 30 seconds. Caregivers must be aware of the possibility that pulseless electrical activity may occur in the depressed newborn.

12. End-tidal CO_2 monitor/indicator to confirm ET tube position after intubation.

D. Preparation of equipment. Upon arrival in the delivery room, check that the transport incubator is plugged in and warm and has a full oxygen tank. The specialist should introduce himself or herself to the obstetrician and anesthesiologist, the mother (if she is awake), and the father (if he is present). While the history or an update is obtained, the following should be done:

1. Ensure that the radiant warmer is on and that dry, warm blankets are available.

2. Turn on the oxygen source or air-oxygen blend and adjust the flow to 5 to 8 L/min. Adjust the oxygen concentration to the desired initial level.

3. Test the flow-inflating bag (if used) for pop-off control and adequate flow. Be sure the proper-sized mask is present.

4. Make sure the laryngoscope light is bright and has an appropriate blade for the anticipated baby (no. 1 for full-term neonates, no. 0 for premature neonates, no. 00 for extremely low birth weight neonates).

5. Set out an appropriate ET tube for the expected birth weight (3.5 mm for full-term infants, 3.0 mm for

premature infants >1,250 g, and 2.5 mm for smaller infants). The NRP recommends a 4.0-mm tube for larger babies, but this is rarely necessary. For all babies, the tube should be 13 cm long. An intubation stylet may be used if the tip is kept at least 0.5 cm from the distal end of the ET tube.

6. If the clinical situation suggests that extensive resuscitation may be needed, the following actions may be required:

a. Set up an umbilical catheterization tray for venous catheterization.

b. Draw up 1:10,000 epinephrine and isotonic saline for catheter flush solution and volume replacement.

c. Check that other potentially necessary drugs are present and ready for administration.

E. Universal precautions. Exposure to blood or other body fluids is inevitable in the delivery room. Universal precautions must be practiced by wearing caps, goggles or glasses, gloves, and impervious gowns until the cord is cut and the newborn is dried and wrapped.

III. DURING DELIVERY. The team should be aware of the type and duration of anesthesia, extent of maternal bleeding, and newly recognized problems such as a nuchal cord or meconium in the amniotic fluid.

A. Immediately following delivery, begin a process of evaluation, decision, and action (resuscitation)

1. Place the newborn on the warming table.

2. Dry the infant completely and discard the wet linens, including those on which the infant is lying. Drying should be thorough but gentle, avoid vigorous rubbing or attempts to clean all blood or vernix from the baby. Ensure that the infant remains warm. Extremely small infants may require extra warming techniques such as wrapping the body and extremities in a plastic wrap or bag or the use of an exothermic mattress.

3. Place the infant with head in midline position, with slight neck extension.

4. Suction the mouth, oropharynx, and nares thoroughly with a suction bulb if there is obvious obstruction or the baby requires positivepressure ventilation. Deep pharyngeal stimulation with a suction catheter may cause arrhythmias that are probably of vagal origin and should be avoided. If meconium-stained amniotic fluid is present, be vigilant for the increased possibility of upper airway obstruction and have equipment for suctioning available (see section IV.A and Chapter 35).

B. Assessment of the need for supplemental oxygen. In the normal fetal environment, oxygen saturation levels are well below those necessary during extrauterine life. These levels do not completely rise to the normal postnatal range for about 10 minutes after birth, and oxygen saturation levels of 70% to 80% are normal for several minutes. During this time, the baby may appear cyanotic, although clinical assessment of cyanosis has been shown to be an unreliable indicator of actual oxyhemoglobin saturation. However, either insufficient or excessive oxygenation can be harmful to the newborn.

1. Pulse oximetry. Several studies have examined the change in oxygen saturation levels in the minutes following birth and have defined percentile ranges for uncompromised babies born at full term. The best defined data have been obtained using readings made at a “preductal” site (i.e., the right upper extremity) in order to avoid the potentially confounding effect of shunting during the transition to an adult-type circulation. Probes specifically designed for neonates can provide reliable readings within 1 to 2 minutes or less; however, oxygen saturation measurements may be unreliable when cardiac output and skin perfusion are poor. It is recommended that oximetry be available for use in the delivery room so that it will be available when

a. Resuscitation can be anticipated, as noted earlier.

b. Positive-pressure ventilation is used for more than a few breaths.

c. Cyanosis is persistent despite interventions.

d. Supplemental oxygen is administered.

C. The concentration of oxygen used to begin resuscitation remains an area of debate. Several trials have shown that survival is improved when resuscitation is initiated with room air compared with 100% oxygen in full-term infants, although there are no studies evaluating other oxygen concentrations. Studies of preterm infants have shown that the use of air or a minimally increased concentration of a blended air-oxygen mixture as the initial gas resulted in an appropriate rise in oxygen saturation levels after birth. Once assisted ventilation or supplemental oxygen use is begun, the oxygen concentration should be adjusted so that the measured preductal oxygen saturation value lies within a specified minute-specific reference range (Table 4.1) as advocated by the NRP. The best available reference is the interquartile range of saturations measured in healthy term babies following vaginal birth at sea level. Different ranges have not been determined for preterm babies or those born via cesarean or vaginal routes.

Because when using these guidelines, the administered oxygen concentration is guided by the measured oxygen saturation, the choice of initial concentration is discretionary, but a uniform approach makes sense.

We use **room air** as the initial concentration for term babies and **21% to 30% oxygen** for premature babies <32 weeks' gestation.

Table 4.1. Target Preductal SPO_2 during the First 10 Minutes after Birth

1 minute	60%-65%
2 minute	65%-70%
3 minute	70%-75%
4 minute	75%-80%
5 minute	80%-85%
10 minute	85%-95%

1. Air should be used if blended oxygen is not available.

2. Oxygen concentration should be increased to 100% if bradycardia (heart rate <60 bpm) does not improve after 90 seconds of resuscitation while employing a lower oxygen concentration.

D. Sequence of intervention. Although Apgar scores (Table 4.2) are assigned at 1 and 5 minutes, resuscitative efforts should begin during the initial neonatal stabilization period. The NRP recommends that at the time of birth, the baby should be assessed by posing three basic questions: (i) Is it a term gestation? (ii) Does the baby have good muscle tone? (iii) Is the baby crying or breathing? If the answer to any of these questions is “no,” the initial steps of resuscitation should commence. In the newly born infant, essentially all

resuscitation problems within the initial postnatal period occur as a result of inadequate respiratory effort or some

obstruction to the airway. Therefore, the initial focus must be on ensuring an adequate airway and adequate breathing.

Table 4.2. Apgar Scoring System

	Score		
Sign	**0**	**1**	**2**
Heart rate	Absent	<100 bpm	>100 bpm
Respiratory effort	Absent	Slow (irregular)	Good crying
Muscle tone	Limp	Some flexion of extremities	Active motion
Reflex irritability	No response	Grimace	Cough or sneeze
Color	Blue, pale	Pink body, blue extremities	All pink

Source: Adapted from Apgar V. A proposal for a new method of evaluation of the newborn infant. *Curr Res Anesth Analg* 1953;32:260-267.

First, assess whether the infant is **breathing spontaneously**. Next, assess whether the **heart rate is >100 bpm**. Finally, evaluate whether the **infant's overall color is pink** (acrocyanosis is normal) or whether the oxygen saturation level is appropriate (see Table 4.1). If any of these three characteristics is abnormal, take immediate steps to correct the deficiency and reevaluate every 15 to 30 seconds until all characteristics are present and stable. In this way, adequate support will be given while overly vigorous interventions are avoided when newborns are making adequate progress on their own. This approach will help avoid complications such as laryngospasm and cardiac arrhythmias from excessive suctioning or pneumothorax from injudicious bagging. Some interventions are required in specific circumstances.

1. Infant breathes spontaneously, heart rate is >100 bpm, and color is judged to be becoming pink (Apgar score of 8 to 10). Under these circumstances, there is no need or indication for directly measuring oxygen saturation. This situation is found in >90% of all term newborns, with a median time to first breath of approximately 10 seconds. Following (or during) warming, drying, positioning, and any necessary oropharyngeal suctioning, the infant should be assessed. If respirations, heart rate, and color are normal, this initial assessment can be done while the infant is placed on mother's chest.

Some newborns do not immediately establish spontaneous respiration but will rapidly respond to tactile stimulation, including vigorous flicking of the soles of the feet or rubbing the back (e.g., cases of **primary apnea**). More vigorous or other techniques of stimulation have no therapeutic value and are potentially harmful. If breathing does not start after **two** attempts at tactile stimulation, the baby should be considered to be in **secondary apnea**, and respiratory support should be initiated. It is better to overdiagnose secondary apnea in this situation than to continue attempts at stimulation that are not successful.

2. Infant breathes spontaneously, heart rate is >100 bpm, but the overall color appears cyanotic (Apgar

score of 5 to 7). This situation is not uncommon and may follow primary apnea. A pulse oximeter should be placed on right upper extremity (usually the hand) as soon as possible after birth. If the measured levels are below the range in Table 4.1 at a specific time after birth, blended blow-by oxygen should be administered beginning with about 30% at a rate of 5 L/min by mask or by tubing held approximately 1 cm from the face. If the saturation improves, the oxygen concentration should be adjusted or gradually withdrawn as indicated to maintain saturation levels in the reference range.

The early initiation of continuous positive airway pressure (CPAP) to a preterm infant who is spontaneously breathing but exhibiting respiratory distress in the delivery room is strongly advocated. In studies of infants born at <29 weeks' gestation, CPAP begun shortly after birth was equally as effective in preventing death or oxygen requirement at 36 weeks' postmenstrual age compared with initial intubation and

mechanical ventilation. Early CPAP use reduced the need for intubation, mechanical ventilation, and exogenous surfactant administration but was associated in one study with a higher incidence of pneumothorax. In spontaneously breathing preterm infants with respiratory distress, use of CPAP in the delivery room is a reasonable alternative to intubation and mechanical ventilation. Using a pressure-regulated means of administration, such as a T-piece resuscitator or ventilator, is preferable. Although individual institutions have preferences regarding CPAP delivery device, there is no evidence that one means of administration is superior.

3. The infant is apneic despite tactile stimulation or has a heart rate of <100 bpm despite apparent respiratory effort (Apgar score of

3 to 4). This represents **secondary apnea** and requires treatment with bag-and-mask ventilation. When starting this intervention, call for assistance if your team is not already present.

A bag of approximately 750 mL volume should be connected to an air-oxygen blend (initial concentration depending on gestational age as in section III.C.) at a rate of 5 to 8 L/min and to a mask of appropriate size. The mask should cover the chin and nose but leave eyes uncovered. After positioning the newborn's head in the midline with slight extension, the initial breath should be delivered at a peak pressure that is adequate to produce appropriate chest rise; often, 20 cm H_2O is effective, but 30 to 40 cm H_2O may be needed in the term infant. This will establish functional residual capacity, and subsequent inflations will be effective at lower inspiratory pressures.

The inspiratory pressures for subsequent breaths should be adjusted to ensure that there is adequate but not excessive chest rise. In infants with normal lungs, this inspiratory pressure is usually no >15 to 20 cm H_2O. In infants with known or suspected disease causing decreased pulmonary compliance, continued inspiratory pressures in excess of 20 cm H_2O may be required. If no chest rise can be achieved despite apparently adequate pressure and no evidence of a mechanical obstruction, intubation should be considered. Especially in premature infants, every effort should be made to use the minimal pressures necessary for chest rise and the maintenance of normal oxygen saturation levels. A rate of 40 to 60 breaths per minute should be used, and the infant should be reassessed in 15 to 30 seconds. It is usually preferable to aim for a rate closer to 40 bpm, as many resuscitators deliver less adequate breaths at higher rates. Support should be continued until respirations are spontaneous, and the heart rate is >100 bpm, but effectiveness can also be gauged by improvements in oxygen saturation and tone before spontaneous respirations are established.

Such moderately depressed infants will be acidotic but generally able to correct this respiratory acidosis spontaneously after respiration is established. This process may take up to several hours, but unless the pH remains <7.25, acidosis does not need further treatment.

a. If positive-pressure ventilation is continued beyond a few breaths, and especially if the infant is intubated, the

use of a T-piece resuscitator (Neopuff Infant T-Piece Resuscitator, Fisher & Paykel Inc, Irvine, CA) enhances the ability to provide consistent pressure-regulated breaths. This is a manually triggered, pressure-limited, and manually cycled device that

is pneumatically powered by a flowmeter. It offers greater control over manual ventilation by delivering breaths of reproducible size (peak and end-expiratory pressures) and a simplified method to control delivered breath rate.

b. Laryngeal masks are easy to insert and are effective for ventilating newborns >2,000 g. They should be considered when bag-and-mask ventilation is not effective and intubation is unsuccessful or no skilled intubator is immediately available. The current models of laryngeal masks are not useful for tracheal suctioning and have not been studied as a means of administering intratracheal medications.

4. The infant is apneic, and the heart rate is <100 bpm despite 30 seconds of assisted ventilation (Apgar score of 0 to 2). If the heart rate is >60 bpm, positive-pressure ventilation should be continued, and the heart rate rechecked in 30 seconds. It is appropriate to carefully assess the effectiveness of support during this time using the following steps.

a. Adequacy of ventilation is the most important and should be assessed by observing chest wall motion at the cephalad portions of the thorax and listening for equal breath sounds laterally over the right and left hemithoraces at the midaxillary lines. The infant should be ventilated at 40 to 60 breaths per minute using the minimum pressure that will move the chest and produce audible breath sounds. Infants with respiratory distress syndrome, pulmonary hypoplasia, or ascites may require higher pressures. The equipment should be checked, and the presence of a good seal between the mask and the infant's face should be quickly ascertained. At the same time, the position of the infant's head should be checked and returned as needed to midline and slight extension. The airway should be cleared as needed.

b. Increase the oxygen concentration to 100% for infants of any gestational age if the resuscitation was started using an air-oxygen blend.

Continue bag-and-mask ventilation and reassess in 15 to 30 seconds. The most important measure of ventilation adequacy is infant response. If, despite good air entry, the heart rate fails to increase and color/oxygen saturation remains poor, intubation should be considered. Air leak (e.g., pneumothorax) should be ruled out (see Chapter 38).

c. Intubation is absolutely indicated only when a diaphragmatic hernia or similar anomaly is suspected or known to exist. The use of an alternate airway is recommended when bag-and-mask ventilation is ineffective, when chest compressions are administered and when an ET tube is needed for emergency administration of drugs, or when the infant requires transportation for more than a short distance after stabilization. Even in these situations, effective ventilation with a bag and mask may be done for long periods, and it is preferred over repeated unsuccessful attempts at intubation or attempts by unsupervised personnel unfamiliar with the procedure. If only inexperienced personnel are available, a laryngeal mask should be considered if an alternate airway is required.

Intubation should be accomplished rapidly by a skilled person. If inadequate ventilation was the sole cause of the bradycardia, successful intubation will result in an increase in heart rate to >100 bpm and a rapid improvement in oxygen saturation. Detection of expiratory

carbon dioxide by a colorimetric detector is an effective means of confirming appropriate tube positioning, especially in the smallest infants.

The key to successful intubation is to correctly position the infant and laryngoscope and to know the anatomic landmarks. If the baby's chin, sternum, and umbilicus are all lined up in a single plane and if, after insertion into

the infant's mouth, the laryngoscope handle and blade are aligned in that plane and lifted vertically at approximately a 60-degree angle to the baby's chest, only one of four anatomic landmarks will be visible to the intubator: From cephalad to caudad, these include the posterior tongue, the vallecula and epiglottis, the larynx (trachea and vocal cords), or the esophagus. The successful intubator will view the laryngoscope tip and a landmark and should then know whether the landmark being observed is cephalad or caudad to the larynx. The intubator can adjust the position of the blade by several millimeters and locate the vocal cords. The ET tube can then be inserted under direct visualization (see Chapter 69).

d. Circulation. If, after intubation and 30 seconds of ventilation with 100% oxygen, the heart rate remains <60 bpm, **cardiac massage** should be instituted. The best technique is to encircle the chest with both hands, placing the thumbs together over the lower third of the sternum, with the fingers wrapped around and supporting the back. If the infant is intubated, this can be done effectively while standing at the head of the bed next to the person performing ventilation and encircling the chest with the thumbs pointing toward the infant's feet. This approach ensures that other caregivers can access the infant for assessment and/or placement of an umbilical catheter. Alternatively, one can stand at the side of the infant and encircle the chest with both hands, a configuration that is “upside down” from the first method. In either method, compress the sternum about onethird the diameter of the chest at a rate of 90 times per minute in a ratio of three compressions for each breath. Positive-pressure ventilation should be continued at a rate of 30 breaths per minute, interspersed in the period following every third compression. Determine effectiveness of compressions by palpating the femoral, brachial, or umbilical cord pulse.

Periodically (every 45 to 60 seconds), one can briefly suspend both ventilation and compression as heart rate is assessed, but frequent interruptions of compressions will compromise maintenance of systemic and coronary perfusion. If the rate is >60 bpm, chest compression should be discontinued and ventilation continued until respiration is spontaneous. If no improvement is noted, compression and ventilation should be continued.

Infants requiring ventilatory and circulatory support are markedly depressed and require immediate, vigorous resuscitation. This will require at least three trained people working together.

e. Medications. If, despite adequate ventilation with 100% oxygen and chest compressions, a heart rate of >60 bpm has not been achieved by 1 to 2 minutes after delivery, medications such as chronotropic and inotropic agents should be given to support the myocardium, ensure adequate fluid status, and in some situations to correct acidosis. (See Table 4.3 for drugs, indications, and dosages.) Medications provide substrate and stimulation for the heart so that it can support circulation of oxygen and

nutrients to the brain. For rapid calculations, use 1, 2, or 3 kg as the estimate of birth weight.

Table 4.3. Neonatal Resuscitation

			Volume			
Drug/Therapy	**Dose/kg**	**Weight (kg)**	**IV (mL)**	**IT (mL)**	**Method**	**Indication**
Epinephrine 1:10,000 0.1 mg/mL	0.01-0.03	1 2	0.2 0.4	0.6 1.2	Give IV push or IT push.	Asystole or severe

	mg/kg IV 0.03-0.10 mg/kg IT	3 4	0.6 0.8	1.8 2.4	The current IT doses do not require dilution or flushing with saline. Do not give into an artery; **do not mix** with bicarbonate; repeat in 5 min PRN.	bradycardia
Volume expanders Normal saline 5% albumin plasma Whole blood	— 0.1-0.2 mg/kg	1 2 3 4	10 mL 20 mL 30 mL 40 mL		Give IV over 5-10 minutes. Slower in premature infants	Hypotension because of intravascular volume loss (see Chapter 40)
Naloxone (Narcan) 0.4 mg/mL	0.1-0.2 mg/kg	1 2 3 4	0.25-0.50 0.50-1.00 0.75-1.50 1.0-2.0		Give IV push, IM, SQ, or IT; repeat PRN 3 times if no response; **if material narcotic addiction is suspected, do not give;** do not mix with bicarbonate (see Chapter 12).	Narcotic depression
Dopamine	30/60/90 mg/100 mL of solution	—	—		Give as continuous infusion	Hypotension because of poor cardiac output (see Chapter 40)
Cardioversion/defibrillation (see Chapter 41)	1 to 4 J/kg increase 50% each time	—	—		—	Ventricular fibrillation, ventricular tachycardia