Twin pregnancy: Prenatal issues

Authors: Stephen T Chasen, MD, Frank A Chervenak, MD
Section Editors: Charles J Lockwood, MD, MHCM, Deborah Levine, MD
Deputy Editor: Vanessa A Barss, MD, FACOG

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INTRODUCTION — Twin pregnancy is associated with higher rates of almost every potential complication of pregnancy, with the exceptions of postterm pregnancy and macrosomia. The most serious risk is spontaneous preterm delivery, which plays a major role in the increased perinatal mortality and short-term and long-term morbidity observed in these infants. Higher rates of fetal growth restriction and congenital anomalies also contribute to adverse outcome in twin births. In addition, monochorionic twins are at risk for complications unique to these pregnancies, such as twin-twin transfusion syndrome (TTTS), which can be lethal or associated with serious morbidity.

This topic will provide an overview of the antepartum care of women with twin pregnancy. Intrapartum management is reviewed separately. (See "Twin pregnancy: Labor and delivery".)

ROLE OF EARLY ULTRASOUND EXAMINATION — Ultrasound examination is the only safe and reliable method for definitive diagnosis of twin gestation. Early ultrasound assessment also provides accurate estimation of gestational age, which is important in all pregnancies, but particularly important in management of twin pregnancies because of the higher risks for preterm delivery and growth restriction. In addition, chorionicity and amnionicity can be determined by ultrasound examination (see 'Assessment of chorionicity' below). This is critical because monochorionic twins have a shared fetoplacental circulation, which puts them at risk for specific serious pregnancy complications, such as twin-twin transfusion syndrome and twin anemia-polycythemia sequence [1-5]. These complications increase the risk for neurologic morbidity and perinatal mortality in monochorionic twins compared with dichorionic twins [2,3,6-9]. In addition to the complications associated with monochorionic twinning, monoamniotic twins also are at risk for cord entanglement and conjoined twins.

Most pregnant women in resource-rich countries undergo routine screening ultrasound examination. Randomized trials comparing routine ultrasound examination with ultrasound performed only for clinical indications have proven that a significant number of twin pregnancies are not recognized until the third trimester or delivery in women who do not undergo routine ultrasound examination [10,11]. As an example, the RADIUS (Routine Antenatal Diagnostic Imaging with Ultrasound Study) study of over 15,000 pregnant women reported that 38 percent of twin pregnancies remained unrecognized until after 26 weeks of gestation in women who did not have a routine second trimester ultrasound examination, and 13 percent of twins were not diagnosed until delivery [10]. The Helsinki Ultrasound Trial reported similar findings: Approximately 25 percent of twin pregnancies were not identified until after 21 weeks of gestation [11]. In both trials, no twin pregnancies were missed on ultrasound examination.

A policy of routine first or second trimester ultrasound examination would diagnose twin gestations at a time when amnionicity and chorionicity are easily determined [12]. Prenatal ultrasound screening guidelines vary worldwide. In the United States, the American College of Obstetricians and Gynecologists (ACOG) does not endorse routine ultrasound examination because, in a population of women with low-risk pregnancy, routine diagnostic sonography has not resulted in a reduction in perinatal morbidity and mortality or a lower rate of unnecessary interventions in randomized trials [10,11,13]. This may be related to the small numbers of twins in these trials and a lack of a standardized protocol for management of multiple gestations [14]. ACOG endorses ultrasound examination when there are specific indications for imaging, such as when twins are suspected because uterine size is greater than expected for menstrual dates. (See "Routine prenatal ultrasonography as a screening tool".)

Assessment of chorionicity — Ultrasonography is an effective prenatal tool for determining amnionicity and chorionicity. The optimal time for performing the ultrasound examination is in the first trimester after 7 weeks (sensitivity ≥98 percent [15]), with lower but acceptable accuracy in the early second trimester (sensitivity ≥90 percent [15]) [16-22]. Sonographic assessment of the fetal membranes is more difficult and less accurate in the third trimester, especially in the setting of oligohydramnios.

- Identification of two separate placentas is a highly reliable indicator of dichorionic twins. This indicator is generally only useful in early pregnancy since separate placentas often appear fused later in gestation. Rarely, a monochorionic placenta that is bilobed or has a succenturiate lobe gives the appearance of two separate placentas [23].

- The presence/absence of the intertwin membrane should be determined and its characteristics assessed early in pregnancy.

  - The intertwin membrane is absent in a monochorionic/monoamniotic twin pregnancy. Visualizing the intertwin membrane becomes more difficult with advancing gestational age because of fetal crowding, progressive thinning of the membrane, and, in some cases, development of oligohydramnios in one or both sacs. These factors may lead to a false diagnosis of monochorionic/monoamniotic twins. On the other hand, monochorionic/monoamniotic twins may be misdiagnosed as monochorionic/diamniotic twins when separation of the amnion and chorion is mistaken for an intertwin membrane.

  - An intertwin membrane with the "twin peak" or "lambda" sign indicates dichorionic twins. The twin peak or lambda sign refers to a triangular projection of tissue that extends between layers of the intertwin membrane from a fused dichorionic placenta (image 1) [24]. It is best seen at 10 to 14 weeks, becomes less prominent after 20 weeks of gestation, and may disappear.

    An additional clue that twins are dichorionic is that the intertwin membrane is thicker with dichorionic than monochorionic twins since the dichorionic/diamniotic membrane consists of four layers (ie, two layers of both amnion and chorion) (image 2), whereas the intertwin membrane in a monochorionic/diamniotic pregnancy only consists of two layers of amnion (image 3). There is no consensus about the cut-off between thin and thick membranes; thresholds of 1.5 to 2 mm in the first trimester have been suggested [20,25]. The difference in membrane thickness is less obvious later in pregnancy [26,27].

- An intertwin membrane with the "T" sign indicates a monochorionic placenta. This sign refers to the appearance of the thin intertwin membrane composed of two amnions as it takes off from the placenta at a 90 degree angle.

- The number of chorion and amnion membrane layers in the intertwin membrane can be counted, but it is technically difficult; therefore, this method is not commonly employed. It is best accomplished between 16 and 24 weeks of gestation using high resolution, magnified images with the membrane perpendicular to the ultrasound beam.

- After the first trimester, identification of fetuses of different sex is a highly reliable means of confirming a dichorionic pregnancy.

In a study including over 600 twin pregnancies at 11 to 14 weeks of gestation at a tertiary referral center, use of the T sign, lambda sign, and number of placentas for determining monochorionicity had sensitivity of 100 percent and specificity of 99.8 percent, with only one dichorionic pregnancy incorrectly assigned as monochorionic [28]. A placental hematoma precluded diagnosis of the T or lambda sign in the incorrectly assigned pregnancy. Other smaller studies have reported sensitivity of 90 to 100 percent and specificity of 97.4 to 99.5 percent using these markers and fetal sex. The lower sensitivities in some studies may be related to assessment very early (<7 weeks) in the first trimester. In a 2016 systematic review of the accuracy of the lambda sign alone (2292 twins, nine studies), sensitivity for predicting dichorionicity was 99 percent (95% CI 98–100) and specificity was 95 percent (95% CI 92–97) [29]. Pooled sensitivity of the absence of the lambda sign for predicting monochorionicity was 96 percent (95% CI 92–98) and pooled specificity was 99 percent (95% CI 98–99).

Other significant findings — In addition to assessment of gestational age, number of fetuses, and amnionicity/chorionicity, first trimester ultrasound examination may detect abnormalities associated with adverse outcome. These include congenital anomalies, crown-rump length discordance (associated with aneuploidy, twin-twin transfusion syndrome [TTTS]), enlarged nuchal translucency (associated with aneuploidy, congenital anomalies, TTTS). (See "Diagnosis and outcome of first-trimester growth delay", section on 'Discordant twins' and "Cystic hygroma and increased nuchal translucency".)

ZYGOSITY AND CHORIONICITY — Dizygotic or "fraternal" twins occur from ovulation and fertilization of two oocytes, which results in dichorionic/diamniotic placentation and two separate placentas. Rare cases of dizygotic twins with monochorionic placentation after assisted reproductive technology (ART) have been reported, with unexplained etiology [30-33].

Monozygotic or "identical" twins result from ovulation and fertilization of a single oocyte, with subsequent division of the zygote. Timing of egg division generally determines placentation (figure 1). Monozygotic twins may have two separate placentas or one placenta that is monochorionic/monoamniotic or monochorionic/diamniotic. However, case reports of atypical twinning (eg, chimeric twins, mirror image twins, discordant monozygotic twins, polar body twins) have prompted hypotheses for other mechanisms of monozygotic twinning [34].

From an imaging perspective, approximately 80 percent of dichorionic placentas are associated with dizygotic twins and 20 percent are associated with monozygotic twins. All monochorionic placentas are associated with monozygotic twins, with the rare exceptions described above in pregnancies conceived by ART.

PREVALENCE AND EPIDEMIOLOGY — Twin births account for approximately 3 percent of live births and 97 percent of multiple births in the United States [35]. Dizygotic twins are more common than monozygotic twins, approximately 70 and 30 percent of twins, respectively (in the absence of use of assisted reproductive technology [ART]) [36]. The prevalence of dizygotic twins varies among populations whereas the prevalence of monozygotic twins is relatively stable worldwide at 3 to 5 per 1000 births.

The major factors influencing the prevalence of dizygotic twins are:

- **Use of fertility stimulating drugs** – Use of fertility enhancing treatments (ART and non-ART) substantially increases the prevalence of twin pregnancy compared with natural conception. These therapies account for most of the increase in twin births in recent years: In the United States twin births increased from 1/53 infants in 1980 to 1/29 infants in 2014 [35]. Over one-third of all twin infants born in the United States can be attributed to iatrogenic interventions (IVF, ovulation induction, superovulation plus intrauterine insemination) [37].

  Dizygotic twins are more common in pregnancies conceived with in vitro fertilization (IVF) than in naturally conceived pregnancies (≥95 percent versus 70 percent) since double embryo transfer is commonly performed as part of IVF [36,38]. Interestingly, IVF also appears to increase the risk of embryo cleavage resulting in monozygotic twins. (See "Pregnancy outcome after assisted reproductive technology", section on 'Monozygotic multiples'.)

  Dizygotic twins are also more common in pregnancies conceived with ovulation inducing agents alone (without IVF) than in naturally conceived pregnancies since these drugs increase the likelihood of ovulation and fertilization of multiple oocytes.

- **Maternal age** – Advancing maternal age is associated with an increased prevalence of twin births. Naturally conceived dizygotic twinning increases fourfold between age 15 and age 35; this may be related to rising follicle stimulating hormone concentration with age [39]. Older women are also more likely to use fertility treatments. One-third of the increase in multiple births in recent decades has been attributed to increasing age at childbirth.

  Although maternal age affects the prevalence of twins, it does not appear to affect pregnancy outcome significantly. When matched for chorionicity, women ≥35 years appear to have the same or a lower risk of adverse perinatal outcome as younger women with twin pregnancies in observational studies [40-45].

- **Race/geographic area** – Significant ethnic/racial variations in the prevalence of naturally conceived dizygotic twins occur worldwide. In one report: 1.3/1000 births in Japan, 8/1000 births in United States and Europe, 50/1000 births in Nigeria [46].

- **Parity** – Increasing parity correlates with an increased likelihood of twin birth, even after adjustment for maternal age [39].

- **Family history** – Twinning appears to have a genetic component that is expressed in women but can be inherited from either parent [47]. Thus, a woman is at increased risk of having twins if she has a family history of twin births. The family history of the biologic father appears to have little or no effect on his partner's risk of having twins; however, he could pass the familial trait to his daughter. This theory is supported by gene mapping studies in animals and humans that found specific genetic mutations expressed by oocytes or ovarian cells were at least partly responsible for twinning [47,48].

- **Maternal weight and height** – Obese (body mass index [BMI] ≥30 kg/m^2) and tall women (≥65 inches [164 cm]) are at greater risk for twin birth than underweight (BMI <20 kg/m^2) and short women (<61 inches [155 cm]) [49-51].

- **Diet** – Diet may be an important factor affecting the twinning rate in some geographic areas, among certain races, and in women of particular body habitus [39,52,53]. As an example, some studies have reported that folic acid supplementation increased the rate of twinning [54]. However, there were several limitations to these studies, which could have biased the results.

RISKS AND OUTCOMES

Risk of early, late, and postnatal loss — Early spontaneous reduction from twin to singleton pregnancy is common, and may be associated with an increased risk of late pregnancy complications [55]. In one study of 549 twin pregnancies, an initial ultrasound examination was performed 3.5 to 4.5 weeks after ovulation and repeated every two weeks until 12 weeks of gestation [56]. Spontaneous reduction of one sac ("vanishing twin") occurred in 27 percent of pregnancies diagnosed as twins prior to 7 weeks of gestation; both sacs were lost in 9 percent. Interestingly, studies have consistently shown that, in pregnancies conceived using assisted reproductive technology (ART), the rate of early loss of the entire pregnancy is significantly lower for twin than singleton gestations [57].

Rates of late fetal and infant death are shown in the table (table 1). Infant mortality in twins is significantly higher than that of singletons (table 2) [58].

Chorionicity and amnionicity also play a role. When both fetuses are alive at 12 weeks of gestation, one study reported the chance of delivering at least one liveborn neonate was 98.2 percent for dichorionic twins, 92.3 percent for monochorionic diamniotic twins, and 66.7 percent for monochorionic monoamniotic twins [59]. The chance of delivering two liveborn neonates was 96.0, 86.2, and 66.7 percent, respectively. The cohort included 3053 dichorionic twins, 544 monochorionic diamniotic twins, and 24 monochorionic monoamniotic twins from a Danish registry.

Fetal complications

All twins — All twin pregnancies have higher rates of the following fetal complications than singleton pregnancies, but lower rates of postterm pregnancy and macrosomia [60]:

- Growth restriction
- Congenital anomalies
- Preterm delivery

Monochorionic twins — The following fetal complications are of particular concern in monochorionic twin pregnancies [1-5]:

- Twin-twin transfusion syndrome (TTTS) – Imbalances in fetoplacental blood flow in the shared placental circulation result in TTTS, which is characterized by oligohydramnios (including anhydramnios) in one amniotic sac and polyhydramnios in the other sac (table 3). The imbalance in volume is caused by anastomotic vessels along the equatorial plate of the placenta. It is a potentially lethal disorder that develops in 10 to 15 percent of monochorionic twins. (See "Twin-twin transfusion syndrome and twin anemia polycythemia sequence: Pathogenesis and diagnosis" and "Twin-twin transfusion syndrome: Management and outcome".)

- Twin anemia-polycythemia sequence (TAPS) – TAPS is a variant of TTTS in which one twin is anemic and the other twin is polycythemic, but without amniotic fluid volume discordance (table 4). The imbalance in red cell shunting is caused by anastomotic vessels at the periphery of the placenta. (See "Twin-twin transfusion syndrome and twin anemia polycythemia sequence: Pathogenesis and diagnosis", section on 'Twin anemia polycythemia sequence'.)

- Twin reversed arterial perfusion sequence (TRAP) – TRAP is a rare complication of monochorionic twins in which a living twin perfuses a nonliving (acardiac) twin through patent vascular channels. (See "Diagnosis and management of twin reversed arterial perfusion (TRAP) sequence".)

- Selective fetal growth restriction due unequal placental sharing (discordance in placental territory) – Selective growth restriction is variously defined as estimated weight of one twin below the 10th percentile or discordance in estimated twin weights greater than 25 percent (discordance = weight larger twin – weight smaller twin/weight larger twin). Selective growth restriction has been classified into three types (table 5).

- Single fetal demise of one twin of a monochorionic pair can cause morbidity or mortality in the co-twin due to their shared placental circulation. (See 'Death of one twin' below.)

- Monochorionic twins have a higher rate of congenital anomalies than dichorionic twins and singletons. The anomalies have a high rate of concordance, but can be discordant. (See 'Screening for congenital anomalies' below.)

Monoamniotic twins — The following fetal complications are of particular concern in monoamniotic twin pregnancies:

- Intertwin cord entanglement (see "Monoamniotic twin pregnancy", section on 'Cord entanglement')

- Conjoined twins – Conjoined twins are classified according to the anatomical site of union (eg, chest, head) with the suffix "pagus" (meaning fixed, eg, thoracopagus). Findings on ultrasound include monoamnionicity, contiguous skin, shared organs, twins that stay in the same orientation to one another, fetal scoliosis, unusual limb positioning, and more than three vessels in the cord [61]. Associated congenital defects unrelated to the area of fusion are common, as is stillbirth. Detailed ultrasonography and echocardiography, possibly with additional magnetic resonance imaging, are essential to determine the extent of deformity, to counsel the parents about prognosis, and to prepare for possible postnatal surgical management [61-64]. Delivery of potentially viable infants is always by cesarean. (See "Monoamniotic twin pregnancy", section on 'Conjoined twins'.)

Maternal risks and complications — Although women carrying twins are at higher risk for some adverse outcomes than women carrying singletons [65], chorionicity does not appear to impact this risk in most studies [66,67].

- **Maternal hemodynamic changes** -- Twin pregnancy results in greater maternal hemodynamic changes than singleton pregnancy [68-71]. Women carrying twins have a 20 percent higher cardiac output and 10 to 20 percent greater increase in plasma volume than women with singleton pregnancy, which increases their risk of pulmonary edema when other risk factors are also present [68,69]. Physiological anemia is common, even though red cell mass increases more in twin pregnancy than in singleton pregnancy.

- **Gestational hypertension and preeclampsia** – Gestational hypertension and preeclampsia are more common in women carrying twins. In a secondary analysis of prospective data from women with twin (n = 684) and singleton (n = 2946) gestations enrolled in multicenter trials of low-dose aspirin for prevention of preeclampsia, rates of gestational hypertension and preeclampsia were twice as high in twin compared with singleton pregnancies (13 percent in twins versus 5 to 6 percent in singletons for both disorders) [72]. Early severe preeclampsia and HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelets) tended to occur more frequently in multiple gestations.

  Zygosity did not impact risk for preeclampsia in a population-based study [73].

  The diagnosis, management, and course of preeclampsia/gestational hypertension are not usually affected by the multiple gestation [74], with some exceptions. A number of studies have reported that maternal uric acid concentration increases with the number of fetuses in both normotensive and preeclamptic pregnancies, with typical values of 5.2 and 6.4 mg/dL, respectively, in twin pregnancies [75-78]. In addition, case reports have described resolution of early severe preeclampsia upon death of one twin [79-81]. (See "Preeclampsia: Clinical features and diagnosis" and "Preeclampsia: Management and prognosis" and "Gestational hypertension" and "Management of hypertension in pregnant and postpartum women".)

- **Gestational diabetes** – Whether gestational diabetes is more common in twin pregnancies is unclear [82-86]. Diagnosis and management are similar to that in singleton pregnancy. (See "Diabetes mellitus in pregnancy: Screening and diagnosis" and "Gestational diabetes mellitus: Glycemic control and maternal prognosis".)

- **Acute fatty liver** – Acute fatty liver is rare but occurs more frequently in multiple than singleton gestations. (See "Acute fatty liver of pregnancy".)

- **Other** – Other maternal disorders observed more often in women with multiple gestations include pruritic urticarial papules and plaques of pregnancy (PUPPP), intrahepatic cholestasis of pregnancy, iron deficiency anemia, hyperemesis gravidarum, and thromboembolism [87,88]. The increased risk of thrombosis relates, at least in part, to the increased prevalence of cesarean delivery and bedrest in these pregnancies. (See "Dermatoses of pregnancy" and "Deep vein thrombosis in pregnancy: Epidemiology, pathogenesis, and diagnosis" and "Intrahepatic cholestasis of pregnancy" and "Treatment and outcome of nausea and vomiting of pregnancy".)

Comparative outcomes of singleton, twin, and triplet pregnancy — Comparative outcomes (other than death) of twin versus singleton and triplet pregnancies are shown in the table (table 6).

PREGNANCY COUNSELING AND MANAGEMENT — Our approach to counseling and management of women with twin pregnancies is described below, and is generally consistent with recommendations of major organizations worldwide (see 'Guidelines from national organizations' below). Clinicians who provide care for these women should be knowledgeable about the issues involved. However, specialized antenatal clinics for women with multiple gestations have not been proven to improve birth outcomes compared with standard care, although data from randomized trials are sparse [89].

Gestational weight gain — The Institute of Medicine recommends the following cumulative weight gain by term for women carrying twins [90]:

- Body mass index (BMI) <18.5 kg/m^2 (underweight) – no recommendation due to insufficient data
- BMI 18.5 to 24.9 kg/m^2 (normal weight) – weight gain 37 to 54 lbs (16.8 to 24.5 kg)
- BMI 25.0 to 29.9 kg/m^2 (overweight) – weight gain 31 to 50 lbs (14.1 to 22.7 kg)
- BMI ≥30.0 kg/m^2 (obese) – weight gain 25 to 42 lbs (11.4 to 19.1 kg)

These thresholds represent the 25th through 75th percentile weight gains in women who gave birth to twins weighing at least 2500 g [90]. In cohort studies, women with normal prepregnancy BMIs who met or exceeded these guidelines had fewer preterm births and higher birth weights compared with women who did not meet the minimum weight gain suggested by the guidelines [91,92]. Poor gestational weight gain after 20 weeks appears to have a greater impact than poor first trimester weight gain [93]. Other guidelines have also been developed [94].

To achieve appropriate gestational weight gain, a normal weight woman needs to increase her dietary intake by approximately 300 kcal/day above that for a singleton pregnancy or 600 kcal/day above that of a nonpregnant woman. After 20 weeks of gestation, weight gain should be approximately 1.75 pounds/week for underweight women and approximately 1.5 pounds/week for normal weight women, with the same or slightly lower weekly weight gain in overweight and obese women.

Vitamins and minerals — Dietary or vitamin/mineral supplementation should include adequate iron and folic acid. Women with twins are at increased risk of developing anemia. The Society of Maternal-Fetal Medicine recommendations for daily total intake of vitamins and minerals in twin pregnancy include [95]:

- Folic acid – 1 mg throughout pregnancy
- Iron – 30 mg throughout pregnancy

We check hematocrit in the first trimester and repeat testing early in the third trimester. We increase iron to 60 mg/day in anemic women.

Screening for Down syndrome — Monozygotic twins are thought to have the same Down syndrome risk per pregnancy as maternal age–matched singletons, and dizygotic twin pregnancies are thought to have twice the risk of at least one affected fetus as maternal age–matched singleton pregnancies. However, observed rates of Down syndrome are lower than expected, possibly due to an increased frequency of early fetal loss [96]. Despite this observation, more data are needed before Down syndrome risk estimates can be adjusted for women with twin pregnancies.

- **Combined test** — We suggest offering Down syndrome screening with the first-trimester combined test, which can provide fetus-specific risk assessment. Increased nuchal translucency at >10 and <14 weeks of gestation is a marker for Down syndrome, other aneuploidies, congenital malformations, and development of twin-twin transfusion syndrome (TTTS). (See "First-trimester combined test and integrated tests for screening for Down syndrome and trisomy 18", section on 'First-trimester combined test'.)

  Maternal serum analyte interpretation is problematic in twin pregnancies since both twins contribute to the analyte concentration and analyte levels may be affected by early loss of one or more embryos of a multiple gestation [97,98]. Measurement of nuchal thickness can improve the detection rate and help identify which fetus is affected [99,100]. In a 2014 systematic review of first trimester combined risk assessment (nuchal translucency and maternal serum analytes) in twin pregnancies, test sensitivity in dichorionic twins was 86 percent (95% CI 73-94) and test sensitivity in monochorionic twins was 87 percent (95% CI 53-98) [101]. In our institution, first-trimester combined risk assessment identified all six affected pregnancies (five discordant and one concordant for Down syndrome) at a screen-positive rate of 5 percent, while nuchal translucency alone detected five of six affected fetuses [100]. Although biochemical testing enhanced risk assessment, serum analyte levels in affected twin pregnancies were closer to the median levels than in affected singleton pregnancies.

Of note, the false-positive rate of nuchal translucency screening is higher in monochorionic than in dichorionic twins because increased nuchal translucency can be an early manifestation of TTTS as well as a marker of aneuploidy [102]. Also, in vitro fertilization affects analyte values used in Down syndrome screening and may be considered by some laboratories when calculating screening results in twins conceived by this method [103]. (See "Laboratory issues related to maternal serum screening for Down syndrome", section on 'In vitro fertilization'.)

An additional factor complicating prenatal diagnosis of monozygotic twins is that rarely these twins have different genotypes due to fetal mosaicism or confined placental mosaicism [104-109]. They can also be discordant for X-inactivation in females, differential gene imprinting, and smaller-scale genetic abnormalities, such as microdeletions [110].

Fetuses with the same genotype may have different phenotypes; as an example, only one fetus of twins with Down syndrome may have increased nuchal translucency. In a series of eight monochorionic twin pairs discordant for nuchal translucency who were karyotyped, discordance was a marker for concordant chromosome abnormalities in one twin pair and discordant chromosomal abnormalities in two twin pairs [109]. For these reasons, both fetuses of a monozygotic pair should be karyotyped when karyotyping is performed, although this may not be possible with chorionic villus biopsy. In some cases, amniocytes, as well as fetal blood, may be needed to make an accurate diagnosis.

- **Noninvasive screening using cell free DNA** — Noninvasive prenatal screening for Down syndrome using cell free DNA is challenging because the fetal cell free DNA in the maternal circulation derives from each fetus. Testing is commercially available for trisomies 13, 18, and 21, although less validation data are available from twin gestations than from singletons [111-114]. Because it is impossible to determine which twin is abnormal based on cell free DNA analysis alone, results are reported for the entire pregnancy, and invasive testing is required to distinguish which twin, if either one, is affected.

  An additional challenge in twin pregnancy is that the amount of cell free DNA contributed by each twin is lower than in a singleton pregnancy and may be quite different for the two fetuses in dizygotic twins [115]. One approach, therefore, is to modify the algorithm used for singleton pregnancies to estimate the smallest fetal fraction contribution of the two fetuses, which involves identifying nonpolymorphic and polymorphic loci where fetal alleles differ from maternal alleles [116].

Diagnostic testing — Diagnostic testing for fetal aneuploidy is discussed separately. (See "Diagnostic amniocentesis", section on 'Multiple gestation' and "Chorionic villus sampling", section on 'Multiple gestations'.)

Screening for congenital anomalies — We suggest an anatomic survey at 18 to 22 weeks of gestation [15]. The incidence of congenital anomalies is three- to fivefold higher in monozygotic twins than in singletons or dizygotic twins, and higher in monochorionic monozygotic twins than in dichorionic monozygotic twins [36,117-120]. The concordance rate of major congenital malformations in monozygotic twins is approximately 20 percent [121]. Dizygotic twins have a similar congenital anomaly rate as singletons and the anomalies have a low concordance rate.

Twins are not predisposed to any specific type of congenital anomaly, although congenital heart disease is more prevalent in monochorionic twins, particularly those with TTTS [118]. In addition to an anatomic survey at 18 to 20 weeks of gestation, fetal echocardiography is suggested at 18 to 22 weeks because 5 to 7.5 percent of monochorionic twins referred for routine fetal echocardiography have congenital heart disease in at least one twin [122-124].

The reported accuracy of ultrasound for detection of fetal anomalies in twins varies because of differences in ascertainment postnatally and at pregnancy termination, criteria for defining an anomaly, and operator capability. Ultrasound examination can detect the majority of major malformations in twins, but should be performed by sonographers experienced in both anomaly detection and assessment of multiple gestation.

The diagnosis of a congenital anomaly in one twin is especially problematic since decisions regarding monitoring, therapy, and delivery affect both fetuses. Expectant management, pregnancy termination, and selective feticide should all be discussed, if appropriate for the type of abnormality and gestational age. Women who choose to continue the pregnancy should understand how the anomalous fetus might affect the co-twin's outcome (eg, preterm birth, organ damage), including the role of chorionicity.

Selective termination of the anomalous fetus with dichorionic placentation is a safe and effective option in expert hands, although there is a risk of miscarriage or preterm delivery of the normal co-twin. Because of these risks, expectant management may be a safer option if the twin with the anomaly is not expected to have prolonged survival or a favorable outcome (eg, trisomy 18) [125]. Anencephaly is an exception since it is associated with polyhydramnios and preterm birth. If polyhydramnios develops in the anencephalic twin's sac, selective feticide or amniodrainage appears to result in longer gestation and higher birthweight in the viable twin than expectant management [126,127]. In our practice, we suggest selective termination whenever a fetal anomaly incompatible with survival is identified in one twin if this anomaly is associated with polyhydramnios. We do not recommend amnioreduction unless maternal respiratory compromise is present.

In monochorionic twins, selective feticide is performed by obstructing one umbilical cord (eg, radiofrequency or laser ablation, bipolar coagulation, ligation) rather than intravascular injection of potassium chloride or digoxin to reduce risk to the co-twin associated with shared circulations [128,129]. (See "Multifetal pregnancy reduction and selective termination", section on 'Selective termination'.)

Monitoring in the second/third trimesters — Because monochorionic twin pregnancies are associated with greater and different risks than dichorionic twins pregnancies, monitoring is based, in part, on chorionicity, and protocols for monochorionic twins have involved more intensive surveillance than protocols for dichorionic twins (see 'Monochorionic twins' below). In a population-based study including over 9000 twins, stillbirth rates were significantly higher in monochorionic than dichorionic twins: 44.4 versus 12.2 per 1000 births (relative risk [RR] 3.6; 95% CI: 2.6-5.1); neonatal death rates also were significantly higher: 32.4 versus 21.4 per 1000 live births (RR 1.5;

95% CI 1.04-2.2) [8]. In other series of monochorionic twin pregnancies, fetal mortality ranged from 6 to 13 percent; most deaths occurred before 24 weeks [2,6,7,130]. After this stage, a systematic review found the prospective risk of fetal death per pregnancy was lower (<2.5 percent) but remained at least threefold higher in monochorionic than dichorionic pregnancies [131].

Monochorionic monoamniotic twins are at highest risk of adverse outcome; management of these pregnancies is reviewed separately. (See "Monoamniotic twin pregnancy".)

It is important to accurately identify each twin consistently over serial examinations. This is relatively easy to do when the twins are of different sexes. In same-sex twins, each twin is identified based on its orientation relative to the other twin: left or right lateral for twins positioned next to each other and top (fundal) or bottom (cervical) for twins positioned vertically. The presenting twin in laterally oriented twins may appear to change over time, but the bottom twin of vertically oriented twins is likely to remain the presenting twin throughout pregnancy [132]. Documentation of the sites of placental implantation (anterior, posterior, lateral) and of the sites and types of placental cord insertion (eg, marginal versus central; normal versus velamentous) is also useful.

Evaluation of fetal growth and growth discordance — Evaluation of fetal growth is particularly important in twin pregnancy because growth restriction and prematurity are major causes of the higher morbidity/mortality rates in twins compared with singleton gestations [3,133-140]. Neurologic morbidity is a major concern, and has several etiologies (eg, prematurity, hemodynamic effects from death of one twin, growth restriction, twin-twin transfusion syndrome) [141].

In the first and second trimesters, the growth rate of twins is not significantly different from that of singletons [142]. In the third trimester, particularly after 30 to 32 weeks of gestation, most studies have described slower fetal growth in uncomplicated twin pregnancies than in uncomplicated singleton gestations [142,143]. A prospective cohort study reported that almost 40 percent of dichorionic twins near term would be classified as small for gestational age when a singleton growth standard is used [143]. The slower growth rate has been attributed to anomalous umbilical cord insertion and to placental crowding (poor early development due to placental proximity).

Growth curves have been derived specifically for twins but are of limited usefulness since they were derived from small populations and did not consider chorionicity or outcome. We and others feel that singleton growth curves are the best predictor of adverse outcome in twin pregnancies and should be used for evaluating twins for growth abnormalities [144].

Twin growth should be monitored with serial ultrasound examinations. Discordance in crown rump length may be observed as early as the first trimester and predicts later weight discordance (see "Diagnosis and outcome of first-trimester growth delay", section on 'Discordant twins'). Discordance in biometric measurements associated with adverse obstetric and neonatal outcome may be noted as early as approximately 18 weeks of gestation [145,146].

We recommend serial ultrasound examinations of twin pregnancies in the second and third trimesters to screen for fetal growth restriction and growth discordance, given the risk of adverse outcome associated with these conditions [147-149] (see 'Chorionicity-based follow-up' below). Although the ability of ultrasound to accurately identify discordant twins (sensitivity 23 to 93 percent, specificity 60 to 98 percent) and adverse perinatal outcome is limited [150-154], fundal height determination is insensitive for identifying fetal growth abnormalities in twins. If ultrasound examination identifies growth discordance or growth restriction in either twin, then more intensive fetal monitoring is initiated, as in singletons. (See "Twin-twin transfusion syndrome and twin anemia polycythemia sequence: Pathogenesis and diagnosis" and "Twin-twin transfusion syndrome: Management and outcome" and "Fetal growth restriction: Evaluation and management", section on 'Pregnancy management'.)

Growth abnormalities manifest in three ways: (1) one twin can be small for gestational age, (2) both twins can be small for gestational age, or (3) one twin can be significantly smaller than the other twin (ie, growth discordance) although neither is small for gestational age. In almost two-thirds of discordant twin pairs, the smaller twin has a birth weight <10th percentile [135]. There is no consensus regarding the optimum threshold for defining discordance in twins. Discordance in birth weight ranging from 15 to 40 percent has been considered predictive of adverse outcome [134,136-138,155-158]. We use an estimated weight difference ≥20 percent as the threshold for defining discordance, but ≥25 percent is also commonly used. Approximately 15 percent of twins are ≥20 percent discordant in weight [139].

- A population-based series with 128,168 twin sets reported fetal growth less than the 10th percentile was significantly more common among highly discordant twins than nondiscordant twins, 60 versus 5 percent [137]. In addition, the neonatal mortality rate of the smaller twin increased with increasing discordance: no discordance (3.8/1000 live births), 15 to 19 percent discordance (5.6/1000), 20 to 24 percent discordance (8.5/1000), 25 to 30 percent (18.4/1000), and 30 percent or more (43.4/1000). Large twins of discordant pairs were also at increased risk of neonatal mortality.

- Another population-based series with 269,287 twin births found a significantly increased risk of neonatal death with birth weight discordancy ≥15 percent for same-sex twins (assume 30 percent are monochorionic [155]) and ≥30 percent for those with different sexes [159]. The lower threshold for risk with same-sex twins may be related to complications in monochorionic twinning, whereas opposite-sex twins are, with very rare exception, dichorionic.

There is no convincing evidence that Doppler velocimetry has benefits for detection of growth restriction over the use of ultrasound alone; therefore, routine use of Doppler velocimetry in twin gestations is not recommended [160,161]. However, Doppler ultrasound is useful for monitoring pregnancies in which the diagnosis of growth restriction, discordance, or fetal anemia has been made.

Assessment of fetal well-being — There is no proven benefit from routine use of antepartum fetal testing (nonstress test [NST], biophysical profile [BPP], amniotic fluid volume determination, or Doppler velocimetry) in uncomplicated twin pregnancies. However, antepartum fetal monitoring in twins is widely practiced beginning at 32 weeks of gestation because of the increased risk of stillbirth in twins, particularly monochorionic twins [162]. We begin weekly testing routinely at 32 weeks of gestation in all twin pregnancies, but earlier and/or more frequently if complications, such as fetal growth restriction, develop. In dichorionic twin pregnancies, the American College of Obstetricians and Gynecologists suggests reserving antenatal testing for gestations complicated by maternal or fetal disorders that require antepartum testing, such as fetal growth restriction [163].

Both NSTs and BPPs are reliable in twin gestations [164-166]. (See "Nonstress test and contraction stress test" and "The fetal biophysical profile".)

The best technique to assess amniotic fluid volume in diamniotic twin gestations is uncertain. Subjective assessment of the volume of amniotic fluid in each sac appears to be as accurate as quantitative assessment. (See "Assessment of amniotic fluid volume", section on 'Multifetal pregnancy'.)

Chorionicity-based follow-up

Monochorionic twins — Our approach to monitoring monochorionic twins is outlined in the algorithm (algorithm 1). We suggest monitoring monochorionic/diamniotic pregnancies beginning at 16 to 18 weeks by assessment of amniotic fluid volume and fetal bladder in both twins for early detection of TTTS; we begin measurement of middle cerebral artery peak systolic velocity (MCA-PSV) in both fetuses at 26 to 28 weeks for early detection of twin anemia-polycythemia sequence (TAPS) [167,168], although there is no consensus about routine performance of middle cerebral artery Doppler to assess for TAPS [15,169]. There are inadequate data to determine the optimal frequency of monitoring, but measurement every two to three weeks is reasonable, with more frequent monitoring if abnormalities are detected (eg, discordant amniotic fluid volumes that do not yet meet criteria for stage I TTTS [170]). The diagnosis of TTTS is based on the sonographic finding of oligohydramnios (maximal vertical pocket <2 cm) and polyhydramnios (maximal vertical pocket >8 cm before 20 weeks and >10 cm after 20 weeks) (see "Twin-twin transfusion syndrome and twin anemia polycythemia sequence: Pathogenesis and diagnosis", section on 'Clinical manifestations and diagnosis' and "Twin-twin transfusion syndrome and twin anemia polycythemia sequence: Pathogenesis and diagnosis", section on 'Monitoring for TTTS'). The diagnosis of TAPS is based on MCA-PSV greater than 1.5 multiples of median (MoM) in one twin and less than 0.8 MoM in the other twin. (See "Twin-twin transfusion syndrome and twin anemia polycythemia sequence: Pathogenesis and diagnosis", section on 'Twin anemia polycythemia sequence'.)

Fetal growth is evaluated every two to four weeks when ultrasound is performed to monitor for TTTS and TAPS. Monochorionic placentation is a significant risk factor for discordant growth (see 'Evaluation of fetal growth and growth discordance' above) due to unequal sharing of the placenta or TTTS [6,171-173]. Monochorionic placentation also appears to have a small independent adverse effect on intrauterine growth compared with dichorionic placentation [174].

Dichorionic twins — Close fetal monitoring for TTTS and TAPS is unnecessary in dichorionic twins. We perform an ultrasound examination every four to six weeks after 20 weeks of gestation to monitor fetal growth, as fetal growth deceleration leading to discordancy is optimally detected between 20 and 28 weeks of gestation [171]. Many twin fetuses with growth abnormalities can be identified by 20 to 24 weeks, so if there is no evidence of growth abnormality at that time, then frequent scanning might not be necessary [175]; however, we continue serial ultrasound assessment until delivery. Scanning every two weeks detected more abnormalities that prompted early delivery in one study, but whether this resulted in better perinatal outcomes was not determined [176].

PREVENTION AND MANAGEMENT OF SELECTED PREGNANCY COMPLICATIONS

Death of one twin — Single fetal death in twin pregnancies is not rare. In one series of 3621 twin pregnancies with two live fetuses at the nuchal translucency scan at about 12 weeks of gestation, single fetal death before 22 weeks of gestation occurred in 0.7 percent of dichorionic twin pregnancies and 0.9 percent of monochorionic diamniotic twin pregnancies [59]. Single fetal death at ≥22 weeks occurred in 0.6 percent of dichorionic twin pregnancies and 1.7 percent of monochorionic diamniotic twin pregnancies. Obviously, the frequency of single fetal demise is higher if early losses (before 12 weeks) are included.

Because of the placental vascular anastomoses between monochorionic twins, the intrauterine death of one twin in a monochorionic pregnancy can cause acute hypotension, anemia, and ischemia in the co-twin due to exsanguination into the low pressure vascular system of the deceased twin, resulting in morbidity or death of the co-twin. In a dichorionic pregnancy, death of one twin may reflect an adverse intrauterine environment that could also place the co-twin at risk, but the risk is much lower.

The type and magnitude of these risks were illustrated in a 2011 systematic review of 22 studies that evaluated the prognosis of the co-twin following a single twin death in various clinical settings [177]. Following intrauterine demise of one twin:

- The rates of fetal demise of the co-twin in monochorionic and dichorionic pregnancies were 15 and 3 percent, respectively (odds ratio [OR] 5.24, 95% CI 1.75-15.73).
- The rates of preterm birth in monochorionic and dichorionic pregnancies were 68 and 54 percent, respectively (OR 1.10, 95% CI 0.34-3.51).
- The rates of abnormal postnatal cranial imaging in monochorionic and dichorionic pregnancies were 34 and 16 percent, respectively (OR 3.25, 95% CI 0.66-16.1).
- The rates of neurodevelopmental impairment of the co-twin in monochorionic and dichorionic pregnancies were 26 and 2 percent, respectively (OR 4.81, 95% CI 1.39-16.64).

While the risk to the surviving co-twin in a monochorionic pregnancy is clear when death of one twin occurs late in pregnancy, the risk with death of one twin in the first trimester is unclear. It has been hypothesized that congenital anomalies and cerebral palsy may be attributable to early fetal loss of one conceptus in a twin gestation [178]. A retrospective study using data from the population-based Northern Multiple Pregnancy Register and Northern Congenital Abnormality Survey in the United Kingdom provided support for this theory. The risk of a congenital anomaly in the survivor following loss of a co-conceptus before 16 weeks of gestation was more than twice that in twin births [179]. These data may reflect, at least in part, the known increased risk of concordant and discordant congenital anomalies in monozygotic twins, which may lead to early in utero death of one twin if the anomaly is severe. Prospective studies are needed to clarify these relationships.

Compared with pregnancies conceived as singletons, additional risks to the survivor after demise of one twin include a 120 g reduction in mean birth weight, an increased risk of small for gestational age birth, and an increased risk of preterm birth [46].

Management — The optimal management of pregnancies in which twin is likely to die or has died is unclear.

- **Dichorionic twins** – In dichorionic twins, death of one twin is not, by itself, a strong indication for delivery of the surviving twin. However, if a condition affecting both twins is present (eg, preeclampsia, chorioamnionitis), then close surveillance and timely delivery of the surviving twin are indicated to prevent a second fetal loss.
- **Monochorionic twins** – As discussed above, death of one twin of a monochorionic pair may have direct harmful effects on the survivor because of intertwin vascular anastomoses. The hemodynamic changes that occur upon death of one twin are immediate; therefore, prompt delivery after death to prevent damage to the survivor appears to be futile [180]. When one twin dies prior to viability, our practice is to discuss the option of pregnancy termination,

although, as stated above, the risk to the co-twin is not clear when the death occurs in the first trimester. Ultrasound and magnetic resonance evaluation of the surviving co-twin can identify signs of brain injury, such as white matter lesions or intracranial hemorrhage, which develop over time. However, the ability of imaging studies to predict or exclude fetal brain injury in this setting is unknown.

If fetal assessment after 26 weeks of gestation suggests impending death rather than demise of one twin of a monochorionic pair, we suggest prompt delivery of both twins rather than expectant management given the high risk of neurologic impairment in the surviving co-twin.

It is not necessary to monitor for maternal coagulopathy since it is rare, although a platelet count and fibrinogen level are desirable prior to delivery. Maternal hypofibrinogenemia or disseminated intravascular coagulation following death of one fetus of a multiple gestation has been described in only a few case reports [181-185]. Although some experts have treated these women with a short course of heparin, spontaneous resolution of hypofibrinogenemia occurs without therapy. We only consider heparin therapy if there is active hypofibrinogemia-related bleeding or hypofibrinogemia-related risk of active bleeding (eg, placenta previa, impending labor), or if there are thrombotic complications. We have not seen clinical bleeding with hypofibrinogenemia in this setting. (See "Clinical features, diagnosis, and treatment of disseminated intravascular coagulation in adults".)

Anti-D immune globulin prophylaxis is recommended for Rh(D)-negative women. (See "Prevention of Rhesus (D) alloimmunization in pregnancy", section on 'Prophylaxis after antepartum events associated with placental trauma or disruption of the fetomaternal interface'.)

Preterm labor and delivery — The major source of perinatal morbidity and mortality in twin gestations is spontaneous preterm birth. The increased risk of spontaneous preterm birth in twins versus singletons may be related, at least in part, to differences in myometrial contractility related to increased myometrial distension [186,187]. In the United States, the preterm delivery rate in twins is 59 percent before 37 completed weeks of gestation and 11 percent before 32 completed weeks (55 percent of twins are low birth weight [<2500 g] and 10 percent are very low birth weight [<1500 g]), although not all of the preterm deliveries are spontaneous [35]. Interestingly, male-male twin pairs seem to be at highest risk of preterm birth [188-190]. Other risk factors for preterm birth, including the relationship between prior preterm birth and preterm birth in the current pregnancy, are reviewed separately. (See "Preterm birth: Risk factors and interventions for risk reduction", section on 'History of spontaneous preterm birth'.)

Several studies have reported that neonatal outcome is similar for singletons, twins, and triplets who are matched for gestational age [191,192]. However, actual outcomes are not equivalent because the average length of gestation for singletons, twins, and triplets is approximately 39, 35, and 32 weeks of gestation, respectively.

Multiple gestations that experience spontaneous reduction deliver earlier than nonreduced pregnancies with the same number of fetuses. In one large series, triplet pregnancies that spontaneously reduced to twins had significantly more preterm births <32 weeks than twins that did not originate from a triplet pregnancy (27 versus 12 percent; OR 3.09, 95% CI 1.63-5.87), and the length of gestation was on average 1.5 weeks shorter [193]. The difference between groups in delivery <37 weeks was not statistically significant (83 percent versus 73 percent in twins without spontaneous reduction).

Prediction of preterm labor and delivery — We do not routinely perform any tests in an attempt to identify asymptomatic twin pregnancies at highest risk for preterm labor and delivery. Although an elevated fetal fibronectin level [194-196] or short cervical length on ultrasound examination [197,198] may predict pregnancies at particularly increased risk of preterm delivery, no intervention has been proven to be effective in reducing preterm birth rates and the predictive value is low in asymptomatic patients (table 7). Home uterine activity monitoring (HUAM) effectively detects contractions; however, there are no convincing data that use of HUAM results in an improvement any measure of neonatal outcome [199]. (See "Second-trimester evaluation of cervical length for prediction of spontaneous preterm birth in singleton gestations", section on 'Multiple gestation'.)

Unproven interventions to prevent or delay preterm labor — The authors do not use any of the following interventions in the routine management of twin pregnancies as none has been proven to be effective. All have been evaluated as potential methods for reducing the risk of preterm delivery in asymptomatic twin gestations.

- **Supplemental** progesterone – The evidence does not support routine use of progesterone supplementation to reduce the risk of preterm delivery or death in twin pregnancies. These data are reviewed separately. (See "Progesterone supplementation to reduce the risk of spontaneous preterm birth", section on 'Twin pregnancy'.)

  Whether progesterone supplemental improves pregnancy outcome in selected twin pregnancies, such as those with a short cervix, is under investigation. In a 2017 meta-analysis of individual patient data from six randomized trials of women with twin gestations and midtrimester cervical length ≤25 mm, vaginal progesterone reduced preterm birth <33 weeks compared with no treatment/placebo (relative risk [RR] 0.69, 95% CI 0.51-0.93; 50/159 [31 percent] versus 62/144 [43 percent]) [200]. The relative risks of neonatal death, respiratory distress syndrome, and birth weight <1500 g were also reduced significantly, on average by 30 to 50 percent. Because appropriately powered randomized trials frequently do not confirm the findings of meta-analysis of small trials [201], we would like to see results from a large clinical trial focusing on twin pregnancies before changing clinical practice. If these findings are confirmed in large randomized trials focused on this population, we would consider routine cervical length screening in twin pregnancies and progesterone supplementation in those with a short cervix. (See "Second-trimester evaluation of cervical length for prediction of spontaneous preterm birth in singleton gestations", section on 'Multiple gestation'.)

- **Bedrest** – Systematic reviews of randomized trials of hospitalization or bedrest in twin pregnancies have failed to show that either intervention increases gestational age at delivery [202-204]. Bedrest may be harmful: A population-based cohort study of pregnant women reported that antepartum hospitalization unrelated to delivery was associated with an increased the risk of venous thromboembolism during hospitalization and in the 28 days after discharge [205].

- **Cerclage**

  - Prophylactic cerclage – A 2014 systematic review of randomized trials comparing cervical cerclage with no cervical cerclage in multiple gestations did not provide convincing evidence that cerclage is an effective intervention for preventing preterm birth and reducing perinatal death or neonatal morbidity [206]. Because of the small number of pregnancies in the review, a modest effect cannot be excluded (122 twin pregnancies and 6 triplet pregnancies; cerclage was indicated by obstetric history in two trials [n = 73 pregnancies] and transvaginal ultrasound in three trials [n = 55 pregnancies]). None of the randomized trials in this review included women with physical examination-indicated cerclage.

- Ultrasound-indicated cerclage – A retrospective study limited to twin pregnancies with cervical length ≤25 mm at 16 to 24 weeks reported placement of an ultrasound-indicated cerclage did not increase gestational age at delivery or reduce the rate of spontaneous preterm birth compared with no placement of an ultrasound-indicated cerclage [207]. In the subgroup with cervical length ≤15 mm, the interval from diagnosis to delivery was significantly longer in the cerclage group, with significantly fewer spontaneous preterm births at <34 weeks and a lower rate of neonatal intensive care unit admission. As the subgroup included only 71 pregnancies, data from larger randomized trials are necessary to determine the appropriate role, if any, for ultrasound-indicated cerclage in multiple pregnancy.

- Physical examination-indicated cerclage – Another retrospective study of 76 nonlaboring twin pregnancies with cervical dilation 1 to 4.5 cm at 16 to 24 weeks reported that those managed with cerclage (usually accompanied by indomethacin and antibiotic therapy) had significantly longer latency before delivery (mean difference 6.8 weeks) compared with similar pregnancies managed expectantly without cerclage or medical therapy [208]. Spontaneous preterm births at gestational ages <24 and <34 weeks decreased, with significant improvement in neonatal outcome.

  Based on this study, physical examination-indicated cerclage could be considered in twin pregnancies; however, we will await prospective data prior to recommending cerclage for our patients. This study highlights the need for a randomized trial to assess the value of cerclage in twin pregnancies with cervical dilation before 24 weeks. A randomized trial of sufficient size could better account for potential confounding factors, including prior preterm birth and cervical length. It could also evaluate an entire protocol that, in addition to cerclage, might include amniocentesis to rule out intrauterine infection and treatments such as indomethacin, antibiotics, and progesterone.

- **Tocolytics** – A 2015 systematic review of randomized, placebo-controlled trials concluded there was no convincing evidence that prophylactic oral betamimetics reduced preterm birth in asymptomatic women with twin pregnancies (<37 weeks: RR 0.85, 95% CI 0.65-1.10; <34 weeks: RR 0.47, 95% CI 0.15-1.50) [209].

  Use of tocolytic drugs is indicated for inhibition of symptomatic preterm labor and is discussed separately. (See "Inhibition of acute preterm labor".)

  Women with twin pregnancies appear to be at higher risk of pulmonary edema after administration of beta-adrenergic agents because they have a higher blood volume and lower colloid osmotic pressure than women carrying singletons. Therefore, these drugs should be used judiciously in women with multiple gestations.

- **Pessary in unselected pregnancies** – In two multi-center, randomized trials that included approximately 2000 unselected women with multiple gestations, prophylactic placement of a cervical pessary between 16 and 20 weeks [210] or 20 and 25 weeks [211] of gestation did not reduce preterm birth or poor perinatal outcome compared with no pessary use.

- **Pessary in pregnancies with a short cervix (≤25 mm)** – Use of a pessary may prolong pregnancy in twin pregnancies with a short cervix. In a multi-center randomized trial in Spain, placement of a pessary in twin pregnancies with a short cervix at 18 to 22 weeks reduced the rate of spontaneous preterm birth <34 weeks: 16.2 percent (11/68) versus 39.4 percent (26/66) with expectant management (RR 0.41, 95% CI 0.22-0.76) [212]. This reduction was not associated with a statistical reduction in neonatal morbidity (composite adverse neonatal outcomes: 5.9 percent [8/68] versus 9.1 percent [12/66], RR 0.64, 95% CI 0.27-1.50). Use of a cervical pessary is a reasonable option in twin pregnancies with a short cervix; however, we are not advising our patients to use a pessary because a significant improvement in composite neonatal morbidity has not been established and further study is needed.

Preterm premature rupture of membranes — Premature rupture of membranes typically occurs in the presenting sac but can develop in the nonpresenting twin, especially after invasive procedures (eg, amniocentesis). Several studies have looked at perinatal outcome after preterm premature rupture of membranes (PPROM) in twin versus singleton gestations [213-215]. The largest of these was a retrospective cohort study of 116 twin pregnancies with PPROM ≤36 weeks of gestation and 116 matched singleton pregnancies [213]. Perinatal and neonatal outcomes were similar in the two groups; however, the median latency period was statistically shorter in twins (11.4 versus 19.5 hours). In our series of twin pregnancies with PPROM, 53 percent of twins with PPROM ≥30 weeks of gestation delivered within two days, compared with only 29 percent of patients with PPROM <30 weeks [216].

Another study compared the frequency of chorioamnionitis in the nonpresenting and presenting twins and by placentation [217]. Chorioamnionitis in the nonpresenting twin was significantly less common in dichorionic than in monochorionic twins. Advanced inflammation (defined as chorioamnionitis with funisitis) was significantly less common in the nonpresenting twin than in the presenting twin, but only when the placentas were dichorionic and separate.

General issues in management of PPROM and PROM are discussed separately. (See "Preterm premature (prelabor) rupture of membranes" and "Management of premature rupture of the fetal membranes at term".)

Antenatal corticosteroids for pregnancies at risk of preterm delivery — We use a standard dosing schedule for antenatal corticosteroids for both singleton and multiple gestations believed to be at increased risk for preterm delivery within seven days. (See "Antenatal corticosteroid therapy for reduction of neonatal respiratory morbidity and mortality from preterm delivery", section on 'Multiple gestation'.)

Routine prophylactic administration to all twin pregnancies should be avoided and may have adverse effects [218]. ACOG recommends one course of antenatal corticosteroids to all multiple gestations between 23 and 34 weeks at risk for delivery within seven days, if neonatal resuscitation of a periviable neonate is planned [163]. ACOG also supports use of a single course of rescue steroids in pregnancies <34 weeks at imminent risk of preterm delivery within the next seven days and had a prior course of antenatal corticosteroids at least seven days previously.

Magnesium sulfate for pregnancies at risk for preterm delivery — Magnesium sulfate appears to reduce the severity and risk of cerebral palsy in infants if administered before preterm birth <32 weeks of gestation, regardless of fetal number [163]. (See "Neuroprotective effects of in utero exposure to magnesium sulfate".)

GUIDELINES FROM NATIONAL ORGANIZATIONS — National organizations that provide guidelines for management of multiple gestation include:

- National Institute for Health and Care Excellence (NICE)
- American College of Obstetricians and Gynecologists practice bulletin [163]
- North American Fetal Therapy Network [15,123,219]
- French College of Gynaecologists and Obstetricians [220]
- Fetal imaging: Executive Summary of a Joint Eunice Kennedy Shriver National Institute of Child Health and Human Development, Society for Maternal-Fetal Medicine, American Institute of Ultrasound in Medicine, American College of Obstetricians and Gynecologists, American College of Radiology, Society for Pediatric Radiology, and Society of Radiologists in Ultrasound Fetal Imaging Workshop [221]

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

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

- Basics topics (see "Patient education: Having twins (The Basics)")

SUMMARY AND RECOMMENDATIONS

- Routine ultrasound examination in the first or early second trimester is the best method to ensure early diagnosis of a twin pregnancy, establish an accurate gestational age, and determine chorionicity. (See 'Role of early ultrasound examination' above.)
- The most reliable indicators of dichorionic twins are identification of two separate placentas and male and female fetuses. If there is a single placental mass, chorionicity and amnionicity are determined by identification of an intertwin membrane and examination of this membrane for the twin peak or lambda sign, T sign, thickness, and number of layers. (See 'Assessment of chorionicity' above.)
- Dizygotic (fraternal) twins are more common than monozygotic (identical) twins, approximately 70 and 30 percent of twins, respectively (in the absence of use of assisted reproductive technology [ART]). The prevalence of dizygotic twins varies among populations whereas the prevalence of monozygotic twins is relatively stable worldwide at 3 to 5 per 1000 births. (See 'Zygosity and chorionicity' above and 'Prevalence and epidemiology' above.)
- Spontaneous reduction of one sac ("vanishing twin") has been reported in 27 percent of pregnancies diagnosed as twins prior to 7 weeks of gestation. Rates of late fetal and infant death are shown in the table (table 1). Morbidity and mortality in twins is significantly higher

than in singletons (table 2). (See 'Risk of early, late, and postnatal loss' above and 'Comparative outcomes of singleton, twin, and triplet pregnancy' above.)

- All twin pregnancies are at increased risk of preterm delivery, congenital anomalies, and growth restriction compared with singleton pregnancies, but lower rates of postterm pregnancy and macrosomia. Monochorionic twins are at significantly higher risk of adverse perinatal outcome than dichorionic twins. They are also at risk for unique pregnancy complications, such as twin-twin transfusion syndrome, twin anemia-polycythemia sequence, twin reversed arterial perfusion sequence, and selective intrauterine growth restriction. Monoamniotic twins are at risk for cord entanglement and conjoined twins. (See 'Fetal complications' above.)

- The Institute of Medicine recommends 25 to 54 pounds total weight gain at term for women carrying twins. The lower end of this range is appropriate for obese women, the middle of the range is appropriate for overweight women, and the upper end of the range is appropriate for women of normal weight. (See 'Gestational weight gain' above.)

- For women who choose to undergo screening for Down syndrome, we prefer the first-trimester combined test over other serum screening tests and noninvasive screening using cell free DNA in maternal blood. This test provides early, fetus-specific risk assessment with a lower false positive rate than second trimester tests. Both fetuses should be karyotyped when karyotyping is performed since even monozygotic twins may be discordant. (See 'Screening for Down syndrome' above.)

- The concordance rate of major congenital malformations in monozygotic twins is approximately 20 percent. In addition to a sonographic anatomic survey, fetal echocardiography is suggested at 18 to 22 weeks in monochorionic twins because of their increased risk of congenital heart disease. Each twin of a dizygotic pair has a similar congenital anomaly rate as a singleton and anomalies, if present, have a low concordance rate. (See 'Screening for congenital anomalies' above.)

- Growth restriction is more common in twin than in singleton pregnancy and can be defined in either of two ways (see 'Evaluation of fetal growth and growth discordance' above):

  - Estimated fetal weight below the 10^{th} percentile using singleton growth curves, or

  - Presence of ≥20 percent discordance in estimated fetal weight between the lighter and heavier twin.

- Our approach to monitoring monochorionic twin pregnancies is described in the algorithm (algorithm 1). (See 'Monochorionic twins' above.)

  In dichorionic twin pregnancies, we perform an ultrasound examination every four to six weeks after 20 weeks of gestation as fetal growth deceleration leading to discordancy is optimally detected between 20 and 28 weeks of gestation. (See 'Dichorionic twins' above.)

- We perform weekly testing with nonstress tests and amniotic fluid evaluation or biophysical profile scoring starting at 32 weeks in all twin pregnancies. Testing is performed earlier and/or more frequently if complications, such as fetal growth restriction, develop. (See 'Assessment of fetal well-being' above.)

- Single fetal death after 20 weeks of gestation occurs in approximately 5 percent of twin pregnancies. Because of placental vascular anastomoses between monochorionic twins, the intrauterine death of one twin in a monochorionic twin pregnancy can cause acute hypotension, anemia, and ischemia in its co-twin, resulting in morbidity or death of the co-twin. For this reason, if fetal assessment after 26 weeks of gestation suggests impending death of one twin, we suggest prompt delivery of monochorionic twins rather than expectant management (**Grade 2C**). Prompt delivery is unlikely to benefit the survivor after death of one twin of a dichorionic or monochorionic gestation. (See 'Death of one twin' above.)

- An elevated fetal fibronectin level or short cervical length on ultrasound examination may predict women at particularly increased risk of preterm delivery; however, the predictive value is low in asymptomatic patients. No intervention has been proven to be effective in reducing preterm birth rates in twin pregnancies. (See 'Preterm labor and delivery' above.)

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Topic 6821 Version 109.0

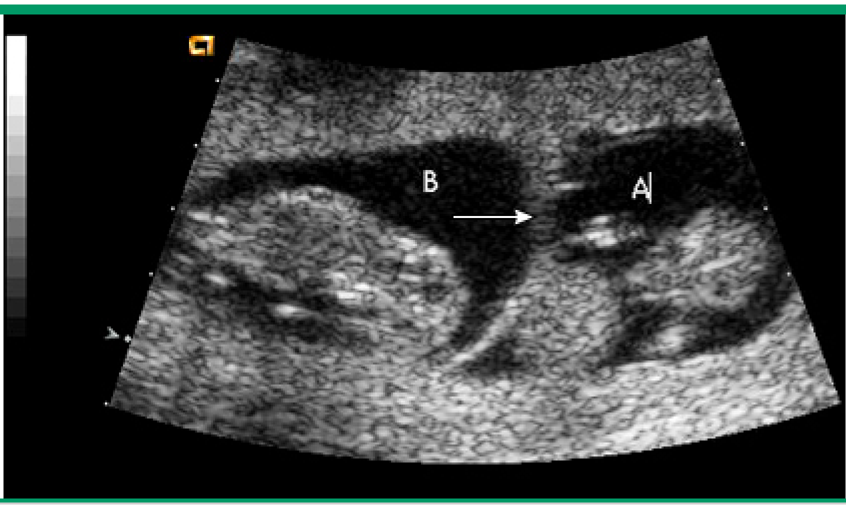
GRAPHICS

Twin peak or lambda sign

The arrow points to a triangular projection of chorionic tissue emanating from fused dichorionic placentas and extending between layers of the intertwin membrane. This is characteristic of a dichorionic diamniotic twin pregnancy.

Graphic 79928 Version 3.0

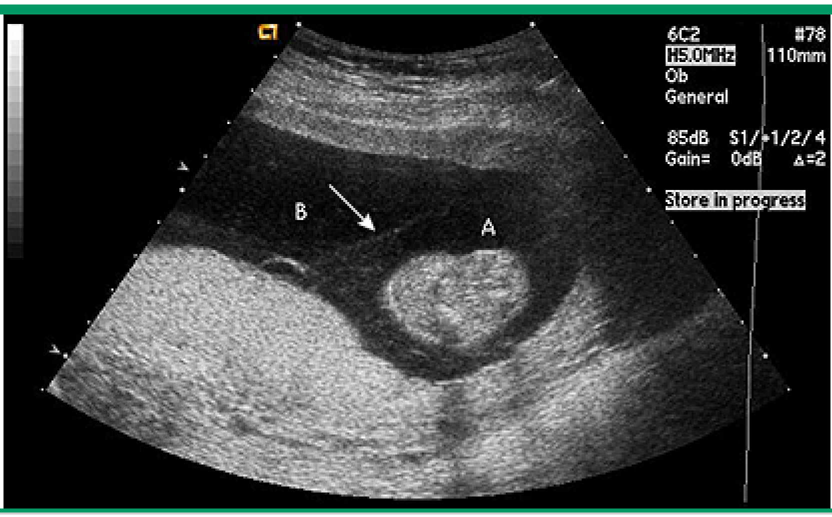
Thick intertwin membrane



The arrow points to a thick intertwin membrane characteristic of a dichorionic twin pregnancy in the first trimester. A and B refer to the two twin sacs.

Graphic 75595 Version 3.0

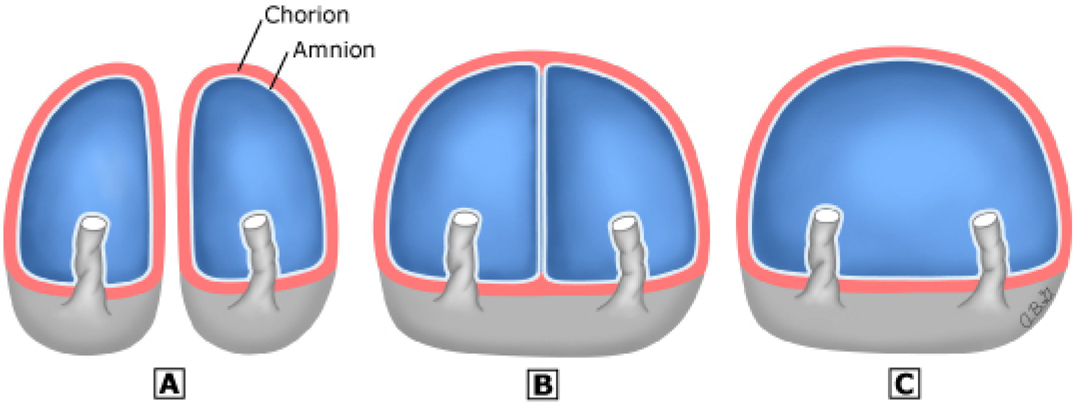
Monochorionic diamniotic pregnancy



The arrow points to a thin intertwin membrane characteristic of monochorionic diamniotic twin pregnancy dividing sac A and sac B.

Graphic 56124 Version 3.0

Placenta and membranes in twin pregnancies



(A) Two placentas, two amnions, two chorions (from either dizygotic twins or monozygotic twins with cleavage of zygote during first three days after fertilization).
(B) One placenta, one chorion, two amnions (monozygotic twins with cleavage of zygote from the fourth to the eighth day after fertilization).
(C) One placenta, one chorion, one amnion (monozygotic twins with cleavage of zygote from the 8^{th} to the 12^{th} day after fertilization).

Graphic 53594 Version 6.0

Fetal and infant death rates in twin gestations (both fetuses alive at 20 weeks of gestation, n=150,386)

Outcome	Percent
Two surviving infants	93.7
One infant death, one surviving infant	2.3
Two infant deaths	1.5
One fetal death, one surviving infant	1.1
Two fetal deaths	1.1
One fetal death, one infant death	0.4

Based upon the Matched Multiple Birth File from the US National Center for Health Statistics. Adapted from Johnson CD, Zhang J. Obstet Gynecol 2002; 99:698.

Graphic 66305 Version 3.0

Infant, neonatal, postnatal mortality per 1000 live births by plurality

	Infant deaths (birth to 1 year)	Neonatal deaths (birth to day 28)	Postneonatal (day 29 to 1 year)
Singletons	11.2	7.8	3.4
Twins	66.4	55.9	10.5
Triplets*	190.4	168.8	21.6

* Triplets and higher order multiple gestations.
Calculated from US Vital Statistics, 1998 and from US Public Health Service. Healthy People 2000: National Health Promotion and Disease Prevention Objectives, DHHS Pub. No. (PHS)90-50212. Washington, DC: US Department of Health and Human Services, Public Health Service; 1990.

Graphic 75320 Version 3.0

Diagnostic criteria for twin-twin transfusion syndrome

▪ Single monochorionic placenta
▪ Polyhydramnios/oligohydramnios sequence • Before 20 weeks of gestation, the maximum vertical pockets for oligohydramnios and polyhydramnios are <2 cm and >8 cm, respectively • After 20 weeks, the maximum vertical pocket for polyhydramnios is defined as >10 cm

Graphic 108158 Version 1.0

Diagnostic criteria for twin anemia-polycythemia sequence

Fetal criteria ▪ MCA-PSV >1.50 MoM in the donor and MCA-PSV <0.80 MoM in the recipient
Neonatal criteria ▪ Intertwin hemoglobin difference >8.0 g/dL and intertwin reticulocyte count ratio (donor/recipient) >1.7

MCA-PSV: middle cerebral artery peak systolic velocity; MoM: multiples of the median.

Graphic 108161 Version 1.0

Diagnosis and classification of selective fetal growth restriction in monochorionic twins

Diagnosis: Estimated weight of one twin below the 10^{th} percentile or discordance in estimated twin weights greater than 25 percent
Type 1: Normal/positive Doppler flow in the umbilical artery ▪ Mild intertwin weight discordance ▪ Usually favorable outcome for both twins: Very low risk of fetal demise of growth-restricted twin
Type 2: Absent/reversed end-diastolic flow in the umbilical artery ▪ Poorest prognosis: High risk of fetal demise of growth-restricted twin ▪ Mean gestational age at delivery: 29 weeks of gestation
Type 3: Intermittent absent/reversed end-diastolic flow in the umbilical artery ▪ Intermediate prognosis: 10 to 15 percent risk of fetal demise of growth-restricted twin ▪ Commonly survive to 32 weeks or more of gestation

Data from: Gratacos E, Ortiz JU, Martinez JM. A systematic approach to the differential diagnosis and management of the complications of monochorionic twin pregnancies. Fetal Diagn Ther 2012; 32:145.

Graphic 108170 Version 1.0

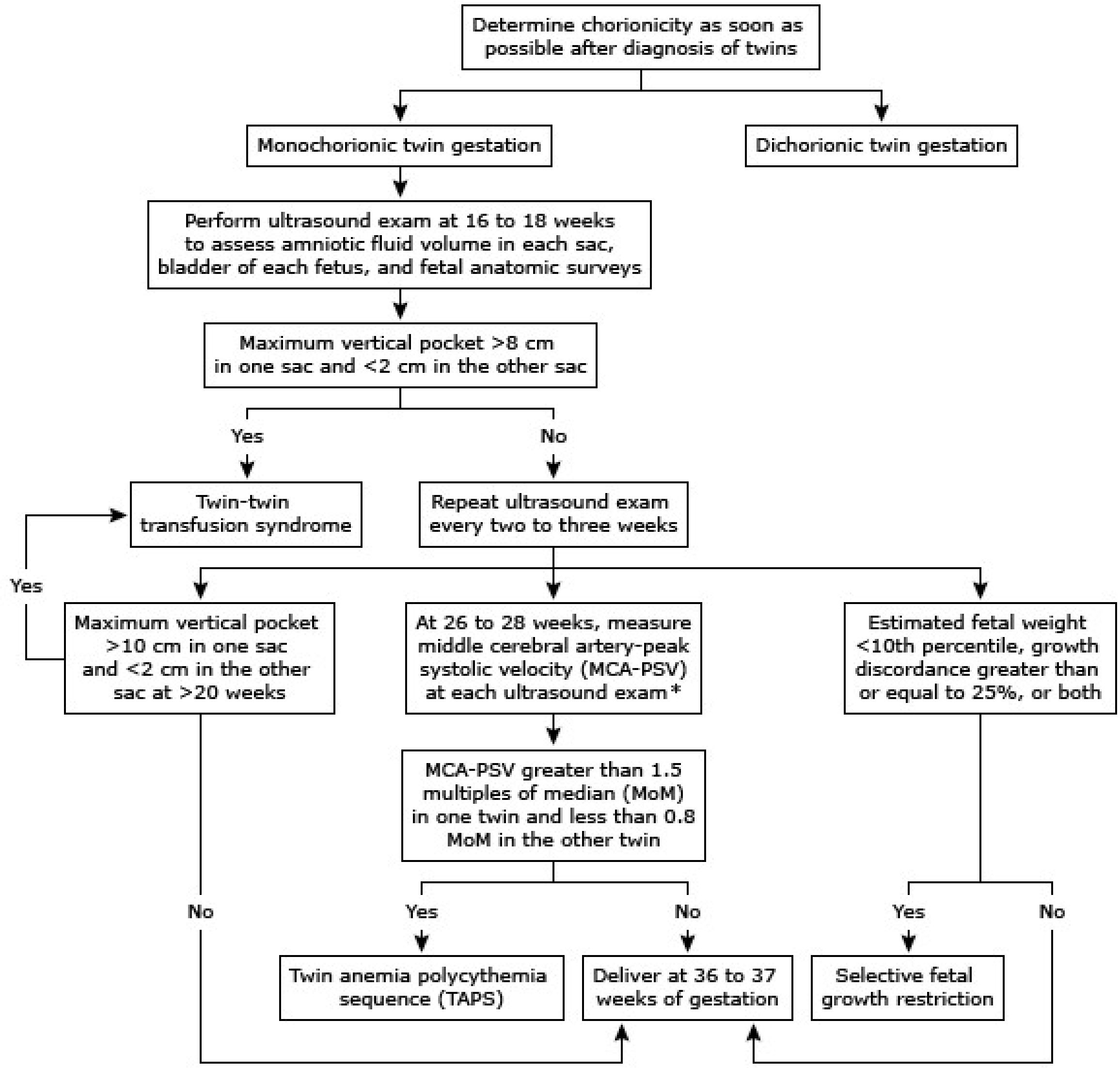
Gestational age and birthweight characteristics of United States singleton, twin, and triplet live births, 2006

	Singletons	Twins	Triplets
No. of births	4,121,930	137,085	6118
Mean gestational age (weeks)	38.7	35.2	32.0
Percent very preterm (<32 weeks)	1.6	12.1	36.3
Percent preterm (<37 weeks)	11.1	60.4	92.6
Birthweight (grams)	3298	2323	1655
Percent very low birthweight (<1500 grams)	1.1	10.2	34.8
Percent low birthweight (<2500 grams)	6.5	57.5	95.4

Adapted from: Martin JA, Hamilton BE, Sutton PD, et al. Births: final data for 2006. Natl Vital Stat Rep 2009; 57:1.

Graphic 60676 Version 4.0

Suggested algorithm for follow-up of monochorionic twins



This algorithm illustrates the authors' approach for monitoring and timing delivery of monochorionic diamniotic twin pregnancies.

* Routine use of MCA-PSV in the third trimester is controversial. Twin-twin transfusion syndrome, twin anemia polycythemia sequence, and selective fetal growth restriction are managed differently (refer to separate topic reviews on each disorder).

Graphic 99508 Version 3.0

Prediction of preterm birth before 32 weeks of gestation in twins by sonographically determined cervical length

Cut-off for cervical length (mm)	Sensitivity (percent)	Specificity (percent)	PPV (percent)	NPV (percent)
Assessment at 21 to 24 weeks of gestation				
20	42	85	22	94
25	54	86	27	95
30	46	89	19	97
Assessment at 25 to 28 weeks of gestation				
20	56	76	16	95
25	63 to 100	70 to 84	13 to 18	96 to 100

PPV: positive predictive value; NPV: negative predictive value.

Data adapted from:
1. Goldenberg RL, Iams JD, Miodovnik M, et al. The preterm prediction study: risk factors in twin gestations. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol 1996; 175:1047.
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Graphic 68816 Version 2.0

Contributor Disclosures

Stephen T Chasen, MD Nothing to disclose **Frank A Chervenak, MD** Nothing to disclose **Charles J Lockwood, MD, MHCM** Consultant/Advisory Boards: Celula [Aneuploidy screening (No current products or drugs in the US)]. **Deborah Levine, MD** Nothing to disclose **Vanessa A Barss, MD, FACOG** Nothing to disclose

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