Twins: prevalence, problems, and preterm births

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On October 10, 2009, there was an article entitled, “21st Century Babies: The Gift of Life, and Its Price,” which started with 2 succinct sentences: “Scary. Like aliens.” The article could have been dismissed easily were it not published in The New York Times and were the topic something other than twins.1 Because this article is the first in a series called ”21st Century Babies: The Twins Dilemma,” twinning will be a part of patient lexicon and a source of concern. Thus, a review of antepartum complications with twin pregnancies is useful not only for the concerned patient but also because recent publications on the topic may influence our practice.

A Google search with the word “twin” yields 116,000,000 results in 0.21 seconds; a PubMed search with the words “twin pregnancy” found 24,982 publications (November 12, 2009). Therefore, although it is not feasible to summarize the voluminous literature on this topic, this review article will focus on: twin birth rate, common antenatal problems, and preterm births, which are the bane of modern obstetrics.

The rate of twin pregnancies in the United States has stabilized at 32 per 1000 births in 2006. Aside from determining chorionicity, first-trimester screening and second-trimester ultrasound scanning should ascertain whether there are structural or chromosomal abnormalities. Compared with singleton births, genetic amniocentesis–related loss at <24 weeks of gestation for twin births is higher (0.9% vs 2.9%, respectively). Selective termination for an anomalous fetus is an option, although the pregnancy loss rate is 7% at experienced centers. For singleton and twin births for African American and white women, approximately 50% of preterm births are indicated; approximately one-third of these births are spontaneous, and 10% of the births occur after preterm premature rupture of membranes. From 1989-2000, the rate of preterm twin births increased, for African American and white women alike, although the perinatal mortality rate has actually decreased. As with singleton births, tocolytics should be used judiciously and only for a limited time (<48 hours) in twin births. Administration of antenatal corticosteroids is an evidence-based recommendation.

Key words: amniocentesis, perinatal mortality rate, preterm birth, twins

Twin birth rate

In the United States, between 1980 and 2006, the twin rate climbed 101% (Figure 1). There were 68,339 twins born in 1980; 27 years later, 137,085 twins were born.2 The twinning rates have also increased in Austria, Finland, Norway, Sweden, Canada, Australia, Hong Kong, Israel, Japan, and Singapore.3 There are multiple causes for the change in the rate of twin pregnancies: use of assisted reproductive techniques (ARTs) and non-ART procedures,4 maternal age, ethnicity, variation among the 50 states, and a decreasing rate of triplets and higher-order multiple gestation.2

Approximately 1% of infants born in the United States in 2006 were conceived with the use of ARTs and account for 18% of the multiple births nationwide. Of 54,566 infants who were born with the use of ARTs, 48% were multiple birth deliveries. The International Committee for Monitoring Assisted Reproductive Technology5 analyzed ARTs for the year 2002 from 53 countries. For conventional in vitro fertilization and intracytoplasmic sperm injection, the overall twin rate was 26%. In the United States, the twin rate was 32%; in Latin America, it was 25%; in Europe, it was 23%; in Asia and the Middle East, it was 22%, and in Australia/New Zealand, it was 21%.

The rate of twin pregnancies varies by maternal age and ethnicity (Figure 2). Between 1980 and 2006, twin birth rates rose 27% for mothers <20 years (compared with 80% for women in their 30s) and 190% for mothers who were ≥40 years old. In 2006, 20% of births to women 45–54 years old were twins, compared with approximately 2% of births to women 20–24 years old. Twin birth rates were essentially unchanged among the 3 largest racial groups for 2005–2006: non-Hispanic white (36.0 per 1000 births in 2006), non-Hispanic black (36.8 per 1000 births), and Hispanic (21.8 per 1000 births). Since 1990, rates have risen 57% for non-Hispanic white and 38% and 21% for non-Hispanic black and Hispanic women, respectively.2

The rate of twin pregnancies also varies among the states (Figure 3). In 2004–2006, the rate of twin pregnancies in the United States was 32.2 per 1000 live births, with <25% being 29.5 per 1000 live births; median, 31.8 per 1000 live births, and >75% being 34.0 per 1000 live births. In Connecticut, Massachusetts, and New Jersey, 4% of all births were twins. In contrast, <2.5% of births to New Mexico residents were twin pregnancies.2

The likelihood of twin pregnancies is also increasing because the rate of trip-
lets and higher-order gestations is decreasing. Thus, twin pregnancies constitute a greater proportion of multiple pregnancies. In 1989, for example, there were 110,670 twin deliveries, which constituted 93.6% of 118,296 multiple births; in 2006, the corresponding numbers were 137,085 twin pregnancies and 95.4%. During these 9 years, the rate of triplets and higher-order gestations decreased by 29%.2

The rapid rise, however, in twin rates over the last several decades may have ended. From 1935-1980, the twinning rate declined. After that, there has been a steady increase: in 1980, the twin rate was 18.9 per 1000 births; in 1990, it was 22.6 per 1000 births, and in 2000, it was 29.3 per 1000 births (Figure 1). The rate reached 32 per 1000 births in 2004 and has stabilized since then; the rate was 32.1 per 1000 births in 2006.2

To summarize, the rate of twin pregnancies varies in the United States for several reasons and has stabilized, despite the recent alarm by public press.1

Identification of chorionicity and anomaly

Because of risks that are associated with monochorionicity, an important aspect of first-trimester ultrasound scans in twin gestation is the determination of chorionicity. It has been demonstrated that chorionicity is best determined by sonography in the first or early second trimester. In a single large tertiary center,6 the sensitivity, specificity, and positive and negative predictive values of prediction of monochorionicity at ≤14 weeks was found to be 89.8%, 99.5%, 97.8%, and 97.5%, respectively. If only 1 placenta is visualized, the presence of an extension of chorionic tissue from the fused dichorionic placentas suggests dichorionicity. If only 1 placenta is visualized, the absence of an extension of chorionic tissue into the intertwin membrane suggests monochorionicity. In monochorionic twin pregnancies, the absence of an intertwin membrane suggests monoamniotic gestation. Monoamniotic diamniotic twin gestation is associated with a 10–15% risk of twin-to-twin transfusion syndrome.7 Although monoamnionicity is somewhat protective against the development of twin-to-twin transfusion syndrome, monoamnionic gestations are associated with a 6% incidence of twin-to-twin transfusion.8

Because of the breadth of the topic, this article will not address risks, associations, or management of unique aspects of monochorionic gestations, namely

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**FIGURE 1**

Twin deliveries and birth rate: United States, 1980-2006

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**FIGURE 2**

Twin birth rate, based on maternal ethnicity and age
twin-to-twin transfusion syndrome and monoamnionicity.

In addition to the determination of chorionicity and amnionicity, the goal of sonographic examination with twin gestations is to identify anomalies and/or syndromes. This should allow for the modification of pregnancy management in efforts to optimize outcome for mother and newborn infants or to identify risk factors that may suggest a need for active or prophylactic therapy to decrease the likelihood of adverse pregnancy outcome. Depending on the severity and/or lethality of the identified anomalies or syndromes, pregnancy management options include (1) continued conservative management, (2) termination of pregnancy in efforts to decrease maternal morbidity and death, especially in cases in which lethal syndromes are suspected, (3) selective reduction to prevent the birth of an adversely affected child and/or to optimize likelihood of survival for an apparently normal fetal sibling, or (4) placental (vascular) and/or fetal and/or neonatal therapy in efforts to optimize outcome for 1 or both the neonates.

Risks that are associated with selective termination of dichorionic twin pregnancies with structural, chromosomal, and Mendelian anomalies are known for centers with experience. Evans et al\textsuperscript{9} reported on 345 cases of selective termination with twins, of whom 7% delivered at \(<24\) weeks of gestation and 93% ended in a viable singleton. Unlike multifetal reduction for multifetal pregnancies, in which outcomes are related to experience,\textsuperscript{10} over 15 years, termination for an anomalous fetus was not associated with improvement in losses or prematurity. The loss rate also was not influenced by the gestational age of the procedure, even when done at \(>24\) weeks of gestation, and by the indication for selective termination.\textsuperscript{9}

For many reasons, the likelihood of aneuploidy is higher in twin pregnancies than in singleton pregnancies. In dizygotic gestations, the background risk for each twin is the same as it would be in a singleton gestation for that mother; however, the number of fetuses results in a 2-fold increase in risk for that gestation when compared with singleton pregnancies. Because ARTs are often used in older women, the risk of aneuploidy should be approximately twice her age-related risk, unless donor oocytes are used. In monozygous twins, the risk of both twins being affected should be similar to that of a singleton gestation.

First-trimester screening for aneuploidy in twin pregnancies has many nuances that limit its capabilities as a screening tool.\textsuperscript{11} Although monoamnionicity has been associated with increased
nuchal translucency, nuchal translucency alone has been shown to be an effective marker for aneuploidy in twin gestations. The addition of serum biochemistry to age and nuchal translucency measurement in twin gestation has a very high sensitivity for detecting trisomy 18 or 21. In that series of 535 sets, maternal (or egg donor) age alone was associated with a 33% detection rate for trisomy 18 or 21. The addition of nuchal translucency increased the sensitivity to 83%; combined age and nuchal translucency and biochemistry (free or total beta human chorionic gonadotropin and pregnancy-associated pregnancy protein A) increased sensitivity to 100%. The authors did acknowledge that, with larger numbers, the combined detection rate would be larger numbers, the combined detection rate would be larger. The authors did acknowledge that, with larger numbers, the combined detection rate would be larger.

As alluded to earlier, early diagnosis is important to minimize the complications that are associated with intervention. Chorionic villus sampling (CVS) is the standard first-trimester approach to the confirmation of suspected aneuploidy. CVS is performed by 2 general approaches: transabdominal vs transcervical, depending on operator experience and placental location/accessibility. In the hands of experienced clinicians, first-trimester CVS has been found to be at least as safe and effective as second-trimester amniocentesis for prenatal diagnosis in twin gestations. De Catte et al summarized the outcomes of CVS with 3 earlier studies and their own experience with 262 cases. Overall outcomes of 614 twins who had CVS were known. The likelihood of total loss was 4.6% (95% confidence interval [CI], 3.5–6.0). Furthermore, Ferrara et al confirmed that CVS does not increase the pregnancy loss rate before multifetal pregnancy reduction.

Compared with singleton pregnancies, twin pregnancy is associated with an increased incidence of anomalies, although the rate of anomalies in dizygotic twins is not likely increased per twin. Hardin et al, for example, compared the prevalence of cardiovascular defects in 56,709 California twin pairs with singleton pregnancies. They categorized cardiac anomalies into 16 groups; twins had a higher incidence for all 16 categories. For 7 of the cardiovascular categories, the prevalence was 2 times higher for twin pregnancies than singleton pregnancies. Like-sex twins, a proxy for monozygosity, had a higher prevalence of cardiac defects than unlike sex twins. Bahtiyar et al reviewed the literature and noted that congenital heart defects were prevalent significantly more among monochorionic, diamniotic twins than the general population (relative risk [RR], 9.18; 95% CI, 5.51–15.29). Ventricular septal defects are the most frequent heart defects.

Fortunately, detection of anomalies in twin gestation does not seem to be compromised by its multifetal nature. Edwards et al confirmed a sensitivity of 82% and negative predictive value of 98% for anatomic surveys among 245 consecutive twins, with a 4.9% prevalence of anomalies. Among 495 monochorionic twins, Sperling et al reported severe structural abnormalities in 2.6%; two-thirds of the abnormalities were cardiac. With first-trimester nuchal translucency and anatomy scan at <20 weeks of gestation, 83% of anomalies and aneuploidy were detected. Earlier reports on detection of congenital anomalies in twin pregnancies noted a lower detection rate.

In 1991, Allen et al reported that, among 157 pair of twins (314 newborn infants), anomalies occurred in 9.5%. Antenatal ultrasonography detected only 39% of all major anomalies, 55% of non-cardiac anomalies, and 69% of major anomalies for which routine prenatal management would be altered. For detection of cardiac anomalies, their ultrasound protocol was limited to a 4-chamber view, and they detected no major cardiac lesions. Thus, it is understandable why the American College of Obstetrics and Gynecology (ACOG) practice bulletin on ultrasonography in pregnancy, every patient should be informed about the limitation of the detection of all major birth defects. If 1 fetus has a major structural or chromosomal abnormality, selective termination should be discussed.

**Genetic amniocentesis**

Compared with singleton pregnancies, twin pregnancies are at higher risk for fetal anomalies and for chromosomal abnormalities. Rodis et al calculated that a 33-year-old woman with twins has an equivalent risk of a child with Down syndrome as a 35-year-old woman with a singleton infant. Thus, the importance of genetic amniocentesis with twins can be seen.

Among the 6 publications that reported on loss rate after genetic amniocentesis with twins, the needle gauge varied, but all investigators used 2 separate needle insertions (Table 1). Although the rate of loss at <24 weeks of gestation varied from 0.4–4.1%, the cumulative experience with >1700 amnio-
Subtypes of preterm birth and perinatal death

Undeniably twin pregnancies are more likely to be delivered preterm (<37 weeks of gestation) than singleton pregnancies, although its magnitude may be underestimated. In 2006, of the 137,085 twins who were delivered in the United States, approximately 60% of the twins were preterm (78,824 infants) and weighed <2500 g (82,799 infants). Approximately 1 in 10 twins was born at <32 weeks of gestation (n = 16,597 infants) or weighed <1500 g (n = 13,983; Figure 4). As Ananth et al noted that, with the exception of France and Finland, most industrialized countries have noted a temporal increase in prematurity. The increase in preterm births is multifactorial but can be categorized into 3 groups: medically indicated because of maternal-neonatal outcomes, after spontaneous onset of preterm labor, and after premature rupture of membranes.

A comparison of the causes of preterm births for singleton vs twin pregnancies is instructive, especially when the data are separated by ethnicity. Using the data from National Center for Health Statistics, Ananth et al provided such data (singleton pregnancies for the year 2000 and twin pregnancies for the years 1999-2002). For singleton and twin pregnancies for African American and white women, the PNM rate is lowest when preterm birth results from spontaneous labor. Within the same ethnicity, the total perterm PNM rate is significantly less for twin than for singleton pregnancies.

The remarkable finding by Ananth et al is that, despite the increase in the rate of prematurity in the United States, there is a concomitant decrease in PNM rates among African American and white women among twin and singleton pregnancies. In 2 separate publications, Ananth et al reported the trends in preterm births for twin and singleton pregnancies in the United States from 1989-2000, along with its impact on

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**TABLE 1**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Country</th>
<th>Twin pregnancy amniocentesis</th>
<th>Needle size</th>
<th>Second puncture</th>
<th>Loss at &lt;24 wk gestation, n</th>
<th>Loss rate, %</th>
<th>Twin pregnancy with no amniocentesis, n</th>
<th>Loss rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yukobowich et al</td>
<td>Israel</td>
<td>476</td>
<td>20</td>
<td>Yes</td>
<td>13</td>
<td>2.7 (1.6–4.6)</td>
<td>477</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>0.6 (0.2–1.8)</td>
</tr>
<tr>
<td>Tóth-Pál et al</td>
<td>Hungary</td>
<td>155</td>
<td>22</td>
<td>Yes</td>
<td>6</td>
<td>3.9 (1.8–9.1)</td>
<td>292</td>
<td>7</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>2.4 (1.1–4.8)</td>
</tr>
<tr>
<td>Millaire et al</td>
<td>Canada</td>
<td>134</td>
<td>22</td>
<td>Yes</td>
<td>4</td>
<td>3.0 (1.1–7.4)</td>
<td>248</td>
<td>2</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>0.8 (0.2–2.8)</td>
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<tr>
<td>Delisle et al</td>
<td>British Columbia</td>
<td>233</td>
<td>No mention</td>
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<td>1</td>
<td>0.4 (0.1–2.3)</td>
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<tr>
<td>Cahili et al</td>
<td>United States</td>
<td>311</td>
<td>22</td>
<td>Yes</td>
<td>9</td>
<td>2.9 (1.5–5.4)</td>
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<tr>
<td>Daskalakis et al</td>
<td>Greece</td>
<td>442</td>
<td>21</td>
<td>Yes</td>
<td>18</td>
<td>4.1 (2.5–6.7)</td>
<td>—</td>
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<td>—</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1751</td>
<td>51</td>
<td></td>
<td>1,017</td>
<td>2.9 (2.3–3.8)</td>
<td>12</td>
<td>1.1 (0.6–2.0)</td>
</tr>
</tbody>
</table>

a Data presented as percentage (95% confidence interval); b Reported loss rate within 4 weeks of birth.

perinatal mortality rates (Figure 7). For their analysis, they had 1,172,405 preterm twin live births and 46,375,578 preterm singleton pregnancies. Over 11 years, the rate of preterm births increased for African American and white twin pregnancies and for white singleton pregnancies; however, it decreased for African American twin singletons. The PNM rate decreased for all 4 groups during the 11 years (Figure 7). The reason for the decrease in the PNM rate is that medically indicated preterm births are associated with a favorable reduction in PNM rates.

Preterm labor: prediction, prevention, and management

Regardless of the temporal trend, the prediction, prevention, and management of preterm birth are important and should be evidence based. Transvaginal cervical length or fetal fibronectin (fFN) level can be used to differentiate those pregnancies that are likely to vs not likely to deliver prematurely.

Fox et al38 described their experience with routinely obtaining, from 22-32 weeks, fFN and measuring transvaginal cervical length. Overall, among 155 twin pregnancies, of which 64% were the result of in vitro fertilization, the rate of birth at <37 weeks of gestation was 53%, at <34 weeks of gestation was 16%, and <28 weeks of gestation was 4%. The rate of spontaneous preterm birth was significantly higher when either fFN was positive or cervical length was <20 mm, but it was the highest when both tests were abnormal (Table 2). It is noteworthy that, if the fFN is negative and cervical length is at least 20 mm, almost 90% of the pregnancies will deliver at ≥34 weeks of gestation. Conversely, if both fFN and cervical length are abnormal, >50% of the pregnancies will deliver at <34 weeks of gestation.

Routine use of the diagnostic tests in twin pregnancies should not be expected to decrease the actual rate of preterm births. Matter of fact, the use of cervical length could increase the duration of antepartum admission without concomitant improvement in neonatal outcome. A retrospective analysis by Gyamfi et al39 compared the outcome among 184 twin pregnancies with cervical length vs 78 pregnancies without this data. Between the 2 groups, there was no difference in gestational age at delivery (34.8 vs 35.3 weeks of gestation; \( P = .35 \)), delivery at <28 weeks of gestation (8.2% vs 3.9%; \( P = .21 \)), or delivery at <34 weeks of gestation (26.1% vs 25.6%; \( P = .94 \)); however, there was an increase in maternal antepartum length of stay (cervical length at 34.5 days vs no cervical length at 31.3 days; \( P < .001 \)). It is uncertain...
whether their findings would have been valid had they obtained fFN measurements in conjunction with cervical length. So, fFN and cervical length can be used to ascertain which twin pregnancies will deliver prematurely, although improvement in peripartum outcomes should not be expected.

Of twin gestations with symptoms of preterm labor, approximately 22–29% of the pregnancies will deliver within 7 days. Thus, the first goal with symptomatic patients should be to identify those who will deliver prematurely. Such identification avoids unnecessary therapeutic interventions like unwarranted hospitalization and medical treatment. The usefulness of fFN in the evaluation of twin gestations with symptoms of preterm labor is not related to its ability to predict who will deliver in the next 14 days (19% positive predictive value; 95% CI, 7–39%), but rather the test’s ability to determine who is not going to deliver during the timeframe (97% negative predictive value; 95% CI, 89–100). The negative predictive value of fFN is similar for singleton and twin pregnancies with symptoms of preterm labor.

Fuchs et al reported on the inverse relationship between cervical length and likelihood of delivery of twin pregnancies within a week of the onset of symptoms: 80% of the pregnancies delivered when the cervical length was 0–5 mm; 46% of the pregnancies delivered when the cervical length was 6–10 mm; 29% of the pregnancies delivered when the cervical length was 11–15 mm; 21% of the pregnancies delivered when the cervical length was 16–20 mm; 7% of the pregnancies delivered when the cervical length was 21–25 mm, and none of the pregnancies delivered when the cervical length was at least 25 mm. Undeniably, randomized trials are needed to determine whether the knowledge of fFN and cervical length influences outcome among twin pregnancies, as it did in the trial reported by Ness et al. While awaiting the results of these randomized trials, we should be cognizant of the ACOG practice bulletin on the management of preterm labor. They recommend that either cervical ultrasound examination or fFN or both diagnostic tests should be
used to determine which patients do not need tocolytics. Until there are publications to the contrary, this recommendation is applicable to twin and singleton pregnancies.

Considering the increased likelihood of preterm births among twin pregnancies, it is reasonable to determine whether it can be prevented. One of the more common interventions that have been tried in the past was the use of prophylactic oral betamimetics to reduce the incidence of preterm birth in twin gestations. From a Cochrane database, Yamasmit et al.\(^44\) reviewed 5 randomized trials with 344 twin pregnancies. This intervention has not been proved to reduce the incidence of birth at <37 weeks of gestation (RR, 0.85; 95% CI, 0.65–1.10) or delivery at <37 weeks of gestation (RR, 0.47; 95% CI, 0.15–1.50). It also has not been shown to change the neonatal outcomes of low birthweight (RR, 1.19; 95% CI, 0.77–1.85) or neonatal mortality rates (RR, 0.80; 95% CI, 0.35–1.82). Therefore, in light of these findings, the use of prophylactic tocolysis should not be undertaken.

Progesterone has been shown to decrease the incidence of recurrent preterm delivery in a singleton gestation.\(^45\) A systematic review by Dodd et al.\(^46\) identified only 2 randomized trials that assessed the use of progesterone vs placebo for multiple pregnancy. Depending on the outcome of interest, the number of participants varied between 154 and 1280. The authors concluded that the use of progesterone in multiple gestations does not decrease the likelihood of birth at <37 weeks of gestation (RR, 1.01; 95% CI, 0.92–1.12), birthweight <2500 g (RR, 0.94; 95% CI, 0.86–1.02), respiratory distress (RR, 1.13; 95% CI, 0.86–1.48), intraventricular hemorrhage grade 3 or 4 (RR, 1.20; 95% CI, 0.40–3.54), necrotizing enterocolitis (RR, 0.77; 95% CI, 0.17–3.42), neonatal sepsis (RR, 0.95; 95% CI, 0.55–1.63), and perinatal death (RR, 1.95; 95% CI, 0.37–10.33).

Another approach to decrease premature births is to reinforce the cervix with a cerclage in multiple gestations. The placement of a cerclage was examined both as a prophylactic intervention and when a short cervix is noted on ultrasound examination. The use of history-indicated (prophylactic) cerclage for ovulation-induced twin gestations (n = 50) in a randomized trial did not decrease the rate of prematurity significantly (45% with cerclage vs 48% without suture) or neonatal mortality (18% vs 15% for suture vs no suture, respectively).\(^47\) More importantly, when cerclage was used in asymptomatic woman with twin gestations and short cervical length on transvaginal ultrasound examination, it significantly increased the risk of delivery at <35 weeks of gestation (75% in the cerclage group and 36% without suture; RR, 2.15; 95% CI, 1.15–4.01).\(^48\) Thus, cerclage of asymptomatic short cervical length should be avoided for twin gestations.

Other prophylactic interventions, which have been examined in multiple gestations to prevent preterm delivery, are bed rest and home uterine monitoring. Crownther,\(^49\) in 2001, summarized the results of 6 trials with hospitalization and bed rest. The summary, which involved >600 patients and 1400 newborn infants, noted that the intervention did not decrease the rate of preterm birth or perinatal mortality. Paradoxically, bed rest significantly (OR, 1.84; 95% CI, 1.01–3.34) increased the risk of preterm birth at <34 weeks of gestation in asymptomatic twin gestations. Similarly a lack of efficacy was also shown with the use of home uterine monitoring for twin gestations. Because home uterine monitoring has not been shown to be beneficial in the prevention of preterm birth in

### TABLE 2

**Spontaneous preterm birth among twin pregnancies**

<table>
<thead>
<tr>
<th>Variable</th>
<th>&lt;28</th>
<th>&lt;30</th>
<th>&lt;32</th>
<th>&lt;34</th>
<th>&lt;37</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative fetal fibronectin level: 135 births, %</td>
<td>21</td>
<td>29</td>
<td>45</td>
<td>&lt;11.5</td>
<td>46</td>
</tr>
<tr>
<td>Positive fetal fibronectin level: 20 births, %</td>
<td>27.3</td>
<td>21.4</td>
<td>35</td>
<td>55</td>
<td>95</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>.005</td>
<td>.017</td>
<td>&lt;.001</td>
<td>.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Transvaginal cervical length ≥20 mm: 129 births, %</td>
<td>2.3</td>
<td>3</td>
<td>4.7</td>
<td>11.9</td>
<td>46.8</td>
</tr>
<tr>
<td>Transvaginal cervical length &lt;20 mm: 26 births, %</td>
<td>25</td>
<td>15.8</td>
<td>26.9</td>
<td>36</td>
<td>83.3</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>.008</td>
<td>.42</td>
<td>.002</td>
<td>.006</td>
<td>.001</td>
</tr>
<tr>
<td>Negative fetal fibronectin level and transvaginal cervical length ≥20 mm: 120 births, %</td>
<td>1.6</td>
<td>2.4</td>
<td>4.2</td>
<td>10.3</td>
<td>43</td>
</tr>
<tr>
<td>Either positive fetal fibronectin level or transvaginal cervical length &lt;20 mm: 24 births, %</td>
<td>13.3</td>
<td>9.5</td>
<td>8.3</td>
<td>26.1</td>
<td>77.3</td>
</tr>
<tr>
<td>Positive fetal fibronectin level and transvaginal cervical length &lt;20 mm: 11 births, %</td>
<td>50</td>
<td>33.3</td>
<td>54.5</td>
<td>54.5</td>
<td>100</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
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<td>&lt;.001</td>
</tr>
</tbody>
</table>

Data derived, with permission, from Fox et al.\(^38\)

multiple gestations, its use should be abandoned.\textsuperscript{50} Thus, the following treatment modalities have no role in the prevention of preterm births with twin gestations: bed rest and oral tocolytics; cerclage and progesterone injections.

One of the most difficult aspects of caring for multiple gestations is the lack of proven intervention once preterm labor has been diagnosed. The use of tocolytics for the treatment of preterm labor has not been shown to decrease the incidence of delivery within 7 days of treatment, perinatal or neonatal death, or the neonatal complications of respiratory distress syndrome, necrotizing enterocolitis, or cerebral palsy. This lack of proven efficacy,\textsuperscript{51} the amplification of colitis, or cerebral palsy. This lack of proven intervention once preterm labor has been diagnosed. The use of tocolytics in multiple gestations\textsuperscript{52} lead ACOG to comment that they should be used judiciously in this population.\textsuperscript{53}

In contrast to the unproven efficacy of tocolytics, the use of antenatal corticosteroids (ACS) has been shown\textsuperscript{54} to decrease the incidence of neonatal death (RR, 0.69; 95\% CI, 0.58–0.81), respiratory distress syndrome (RR, 0.66; 95\% CI, 0.43–0.69), intraventricular hemorrhage (RR, 0.54; 95\% CI, 0.43–0.69), necrotizing enterocolitis (RR, 0.46; 95\% CI, 0.29–0.74), and systemic infections within the first 48 hours of life (RR, 0.56; 95\% CI, 0.38–0.8). Although none of the studies specifically addressed use in multiple gestations, the National Institutes of Health recommends that all women in preterm labor, regardless of the number of fetuses, be given a course of ACS.\textsuperscript{55}

Although ACS does improve neonatal outcome significantly, it should not be administered repeatedly. A retrospective study by Murphy et al\textsuperscript{56} compared the use of prophylactic ACS in twin gestations beginning at 24 weeks of gestation and given every 2 weeks (n = 136) with the standard approach in women who were at immediate risk of preterm delivery (n = 902). The prophylactic approach was shown not to offer a significant reduction in respiratory distress syndrome (13\% vs 11\%; adjusted OR, 0.69; 95\% CI, 0.33–1.46) and was associated with exposing a large number of babies to unnecessary treatment that adversely affects growth. Therefore, the repeated administration of ACS should be avoided in favor of those pregnancies that are at immediate risk for preterm births.

One single rescue course of ACS should be given among twins who have received betamethasone 12 mg, intramuscularly, twice, 24 hours apart. If at least 14 days have elapsed and delivery is likely at <33 weeks of gestation, then a single rescue dose should be administered. This recommendation is based on the randomized trial by Garite et al\textsuperscript{57} that involved 437 patients, with 577 newborn infants, 24\% of whom (141; 1 fetal death before randomization) were from twin gestations. Compared with the patients who received placebo, patients who received the rescue dosage had a significant reduction in composite perinatal neonatal morbidity (64\% vs 44\%; P = .02) and significantly decreased rate of respiratory distress syndrome, ventilator support, and surfactant use.

In summary, although there are diagnostic tests to identify those pregnancies that will deliver prematurely, these tests do not decrease the rate of preterm birth. There are no known treatments to decrease the likelihood of preterm birth. Tocolytics should be used either to transfer a patient to a tertiary center or to ensure ACSs are administered. Prolonged tocolytic use should be avoided, as should repeated administration of corticosteroids.

Comment

Twins are a source of awe and delight to parents, fascination and photo opportunities to the press,\textsuperscript{1} and challenge and trepidation to clinicians.\textsuperscript{58,59} Compared with singleton pregnancies, twin pregnancies are more likely to be complicated by hypertensive disorders, gestational diabetes mellitus, anemia, preterm birth, ante- and postpartum hemorrhage, and maternal death.\textsuperscript{60} The newborn infants from twin pregnancies are more likely to have anomalies,\textsuperscript{26} intrauterine growth restriction,\textsuperscript{61} handicap, and cerebral palsy. The average cost for singleton deliveries is $9,845 and for twins is $37,947.\textsuperscript{60} Thus, continued understanding of twin pregnancies is important.

This review of the literature on twin gestations, although limited to common problems, was notable for 4 findings. First, the rate for twin gestations has stabilized for now. For 2004, 2005, and 2006, there have been approximately 32 twin gestations per 1000 births (Figure 1). Second, the sonographic evaluations of twin gestations should be limited not only to the identification of the choriocytic but also aneuploidy with first-trimester screening and anomaly with first- and second-trimester ultrasound examinations. Because anomalies and aneuploidies are more common with twin pregnancies than with singleton pregnancies,\textsuperscript{26,27} it is important that clinicians who have experience in detecting these abnormalities evaluate these patients. If need be, parents who are expecting twins should be offered and referred for CVS, genetic amniocentesis, and selective reduction.

Third, we found that the rate of preterm births is significantly higher for twin pregnancies than for singleton pregnancies (Figure 4). Although this has been known, findings from the national data provide not only unequivocal evidence but also the magnitude to which this occurs. Data from the United States also are available for the analysis of causes for preterm birth (Figure 5) and associated perinatal mortality rates (Figure 6). But what is most captivating is that, although the rate for preterm birth has increased, the associated perinatal mortality rate has actually decreased. The fact that this conclusion is based on a population-based, retrospective cohort study comprised of 46,375,578 women and 1,172,405 twins in the United States is staggering.\textsuperscript{36,37} It will be beneficial if other countries can confirm the findings reported by Ananth et al\textsuperscript{36,37} and if future studies can ascertain what precisely decreased the perinatal mortality rate. It will also be useful to understand whether the overall perinatal mortality rate, not just for preterm births, has also decreased in the United States.

Fourth, the findings focus on the management of preterm labor with twin gestations. Clinicians should be cognizant
of the facts that, with twins, preterm contrac-
tions are common, that the benefit of toco-
ycolytics is limited although the com-
lications rate is higher, and that the pre-
term birth-related perinatal mortality rate has been lowered. Whenever feasible,
clinicians should use diagnostic tests (transvaginal cervical length or fFN) to
differentiate true vs false preterm labor.
The use of tocolytics should be limited to
(1) either the cervical length is <2.5 cm or fFN is positive or both, (2) the test results have been evaluated, (3) 48 hours have elapsed since the first dosage of corticosteroid was administered, or (4) the patient has been transferred to a tertiary center. As with singleton pregnancies, there is no justification for prolonged toco-
ycolytics with twin pregnancies.

In conclusion, there are several reas-
suring findings with twin pregnancies. The rate of twin pregnancies is not in-
creasing in the United States; although the preterm birth rate is high, the associ-
ated perinatal mortality rate is decreasing. Future studies should focus on im-
proving the detection of birth defects and of abnormal growth and on antepa-
tum testing to improve the outcomes for twin pregnancies with medical or obstet-
ric complications.

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