Original Article

Clinical Dilemma in Triplet Pregnancy: When Is It Appropriate to Intervene for a Jeopardized Fetus?

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OBJECTIVE:

To determine gestational age-specific risks of intervening to ''rescue'' a compromised fetus in triplet pregnancies.

STUDY DESIGN:

We analyzed retrospectively triplet pregnancies managed at New England Medical Center (July 1992–May 2000; $n = 97$ pregnancies). For each week in gestation, we compared the chance of at least one of three infants developing complications of prematurity in Scenario A (delivery at that gestation to rescue the jeopardized fetus) with the chance of at least one of two infants from Scenario B (allowing the jeopardized fetus to die in utero to prolong pregnancy) developing that complication later in gestation.

RESULTS:

We observed a decreased risk of at least one infant developing a specific complication in Scenario B than in Scenario A for all complications studied.

CONCLUSIONS:

Comparison of triplet outcomes with the two surviving older newborns identifies important changes in risk between 25 and 32 weeks. These data enable physicians and parents to weigh acceptable risks with benefits.

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INTRODUCTION

The incidence of triplet pregnancies has risen steadily, primarily because of the development of assisted reproductive technology. The rate of triplets and higher order births increased from 29 per 100,000 live births in 1971 to 174 per 100,000 live births in 1997.[1–5] Although the number of spontaneously conceived triplets increased slightly in the past 30 years, this only accounts for about 10% of the increase in multiple births. The rest is thought to be because of the introduction of the ovulation-inducing drugs in the late 1960s and the advent of the artificial reproductive technology in the 1980s.[1–5] The rise in multiple pregnancies has led to the concomitant increase in low-birth-weight infants born at younger gestational ages.[6] With the increase in the number of infants born at younger gestational ages and smaller birth weights, there is an enhanced risk of one of the fetuses developing severe complications in utero. Some studies postulate that at least 5% of all triplet pregnancies are jeopardized by life-threatening fetal complications in at least one of the fetuses.[7,8] Interventions in such pregnancies to save the jeopardized fetus by immediate delivery may place the remaining fetuses at a significant risk of morbidity and mortality based on prematurity. However, there are no published data available to guide physicians in deciding when it is appropriate to intervene in such pregnancies to rescue the jeopardized fetus while minimally endangering the remaining two fetuses.

Recently, we cared for a triple pregnancy (tri-zygotic) in which one fetus on a routine office ultrasound visit showed early evidence of oligohydramnios and growth restriction at 25 weeks. During the ultrasound, one short deceleration to 80 beats per minute (lasting less than a minute) was observed in this fetus. The mother was admitted for further evaluation and observation of the pregnancy. The perinatologists and Neonatologists together discussed with the parents the possible options in the event of acute decompensation of the jeopardized fetus as manifested by severe decelerations, suggesting its imminent demise unless emergent delivery was undertaken. It was determined that the neonatal risk to the nonjeopardized fetuses was too great if they were delivered at this gestation, so such inervention would not yet be appropriate. This decision was reviewed every few days with the parents. At 28 weeks, there was interval growth of the jeopardized fetus but continuing growth restriction and oligohydramnios. However, the decision at this time was that the risks to the other two fetuses was now sufficiently low that intervention in the event of acute

decompensation of the growth-restricted fetus would be appropriate. Fortunately, the pregnancy progressed further, the mother developed labor at 33 weeks and was delivered by cesarean section of three healthy infants, including one who as growth restricted. The infants had a noneventful neonatal course.

Based on this experience, we determined to study all triplet pregnancies recently cared for and delivered at our institution to develop data which may help in deciding when intervention or nonintervention might be appropriate for a jeopardized triplet fetus. We propose that the comparative evaluation of neonatal risks associated with immediate delivery versus waiting for a more mature gestation (allowing the jeopardized fetus to die) will help in choosing the appropriate therapeutic strategy.

METHODS

This study was a retrospective evaluation of all triplet pregnancies managed and delivered at New England Medical Center (NEMC) from December 1992 to May 2000. Triplets delivered before 24 weeks were excluded from the study. All deliveries and subsequent care for the infants were performed at NEMC. A triplet pregnancy with a known spontaneous fetal death after 24 weeks but before birth was still considered as a triplet pregnancy according to the original number of fetuses. There were four triplet pregnancies that had one in utero fetal demise each. However, as the focus of data collection was on complications in live-born infants, only the live born infants were included in the data analysis. During this time period, there were 287 live births from 97 pregnancies. The gestational age used for the study was that assigned clinically by the attending perinatologist based on conception date (for assisted reproduction pregnancies) or first-trimester ultrasound.

Data on mothers and infants were collected from a review of their medical records, or, for patients whose medical records could not be located (9/97 mothers and 35/287 infants), patient discharge summaries. Data were obtained on 97.5% (280/287) infants and 100% of the mothers. Information relating to a range of intrapartum and neonatal complications was collected; to ensure consistency, all of the information was extracted by a single investigator. The specific information recorded for each infant included perinatal betamethasone treatment of the mother, birth order, mode of delivery, gestational age, birth weight, sex, race, apgar scores at 1 and 5 minutes, respiratory distress syndrome (RDS), surfactant treatment, number of days of intubation, number of days spent on CPAP therapy, number of days of additional oxygen therapy, number of days of steroid therapy, broncho-pulmonary dysplasia (BPD), significant patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), periventricular leukomalacia (PVL), retinopathy of prematurity (ROP), and survival to discharge home. Information recorded for each mother included age, number of pregnancies, number of births, method of conception, reason for cesarean section (if applicable), and complications during pregnancy, including preterm rupture of membranes, preterm labor, anemia, pre-eclampsia, gestational diabetes, diabetes, HELLP, fatty liver syndrome, oligohydramnios of any of the fetuses, and in utero growth retardation (IUGR) of any of the fetuses.

The following definitions were used for neonatal complications. RDS was defined as a diagnosis made specifically by the attending neonatologist based on the need for oxygen therapy beyond the first 24 hours of life with typical radiographic signs.[8] BPD was defined as the need for supplemental oxygen therapy at 28 days with radiographic changes consistent with BPD.[9] A significant PDA was defined as a PDA diagnosed by echocardiographic visualization of a patent ductus, which subsequently required treatment, by either indomethacin or surgical ligation. NEC was defined as radiological evidence of pneumotosis intestinalis, intestinal perforation, or the need for surgery with a confirmation of the diagnosis at the time of surgery.[10] PVL and IVH were defined by the presence of typical ultrasonographic findings as determined by the radiologist. A qualified ophthalmologist defined stages of ROP.

All of the complications were grouped into three categories: survival to discharge, pulmonary complications (RDS and BPD), and nonpulmonary complications (NEC, IVH, PVL, PDA, and ROP). For each gestational week, we compared the relative risk of at least one out of three infants from Scenario A (delivery at that gestation to rescue the jeopardized fetus) of developing specific complications of prematurity with the risk of at least one of two infants from Scenario B (allowing the jeopardized fetus to die in utero to prolong pregnancy for the two surviving fetuses) developing that complication later in gestation.

Summary statistics were calculated using Analyze It software (Microsoft, Redmond, WA). The data for the two scenarios were generated using the data obtained from all of the triplets born in the specified time period. The risk of at least one of the three infants from Scenario A of having a specific complication was calculated using the following equation: $1-(1-x)^3$. The risk of at least one of the two infants from Scenario B of having the same complication was calculated by using the equation: $1-(1-x)^2$, where x was the observed rate of having the complication in the triplet cohort at each gestational age.

RESULTS

The summary data for the 97 triplet pregnancies cared for and delivered at NEMC during the 8-year time period and the 280 of the 287 infants are presented in Table 1. Four of the pregnancies were reduced to triplets from quadruplets in the first trimester. As expected, based on the impact of assisted fertilization, less than 10% were spontaneously conceived. The data for the mean gestational age and birth weight for the infants were consistent with recently published data on cohorts of triplet pregnancies.[12,13] An analysis of deliveries by gestational age interval revealed that

Table 1 Maternal and Neonatal Statistics

	Mean/Median	Range
Maternal age (years)	32.4±4.9	20–53
GA (weeks)	33.5±3.3	24–37
BW (gm)	1804.8±543.4	461–3147
Apgar at 1 minute	8	0–10
Apgar at 5 minutes	9	4–10

GA=gestational age.
BW=birth weight.

Table 2 Neonatal Complications

Complication	Total (%)
Demise	5 (1.8)
Pulmonary complications	
RDS	121 (43.0)
BPD	24 (8.6)
Non-pulmonary complications (NPC)	
PDA	29 (10.4)
IVH	27 (9.6)
Grades 1–2	24 (8.6)
Grades 3–4	3 (1.1)
NEC	8 (2.9)
ROP	17 (6.1)
At least one NPC	58 (20.7)
At least two NPCs	18 (6.4)
No complications	159 (56.8)

Table 3 Inflection Points in Neonatal Complications

	Scenario A (weeks)	Scenario B (weeks)
RDS	31	28
BPD	28	26
2 NPC	27	26

These data are obtained from Figures 2 and 3 and represent the points at which there is a significant decrease in the risk of developing the specific complication.

two-thirds of the mothers delivered after 32 weeks, while less than 5% delivered prior to 26 weeks. While most of the mothers who delivered before 34 weeks received a complete course of betamethasone treatment prior to delivery, only a small percentage of those who delivered after 34 weeks completed a betamethasone treatment prior to delivery, usually as the consequence of treatment for PTL prior to 34 weeks.

The overall neonatal survival rate was 98.2% with deaths occurring only in the extremely premature infants (24 to 26 weeks). Neonatal demise occurred in two out of three infants born at 24 weeks, one out of two infants born at 25 weeks, and two out of seven infants born at 26 weeks. Neonatal mortality and other neonatal complications are summarized in Table 2.

The main focus of this study was the evaluation of risks to live-born infants between strategies of ''deliver now'' and ''deliver later''. This was accomplished by making a comparison between the relative risk that at least one out of three infants would develop a specific complication of prematurity in Scenario A (delivery at that gestation to rescue the jeopardized fetus) with the risk of at least one of two infants from Scenario B (allowing the jeopardized fetus to die in utero to prolong pregnancy for the two surviving fetuses) developing that complication when born later in gestation. In order to do this, we generated relative risk plots for at least one of the infants for developing a specific complication for each gestational age within each scenario. We constructed these curves for neonatal demise (Figure 1), each of the pulmonary complications (Figure 2a and b), and the chance of having at least two of the non-pulmonary complications (Figure 3). Given that one of the fetuses is jeopardized at a specific gestational age, each point on the Scenario A plot represents the chance of at least one of the three infants developing a specific complication if all three fetuses are delivered at that specific gestational age. In contrast, each point on the plot for Scenario B represents the chance of at least one of the two infants developing that same complication, allowing the compromised fetus to die in utero at that gestational age and the remaining two infants then delivered at least 1 week after that specific gestational age. The comparison between the two scenarios for each of the complications (neonatal demise, pulmonary and nonpulmonary complications) was based on the differences between the apparent inflection points after which the chance of developing the specific complications significantly declined in that scenario.

Significant declines in the risk for developing a specific complication occurred at different gestational ages for infants from Scenario A and those from Scenario B. The inflection point for the probability of at least one infant of developing RDS in Scenario B occurred at 28 weeks, whereas in Scenario A, the decline did not occur until 31 weeks gestation (Figure 2a). The inflection point for the risk of at least one infant developing BPD in Scenario B occurred after 26 weeks, while in Scenario A, the drop off only happened after 28 weeks (Figure 2b). The inflection point for at least one of the fetuses of developing at least two of the nonpulmonary complications occurred at 26 weeks for Scenario B, and for Scenario A, it occurred at 27 weeks (Figure 3).

DISCUSSION

Multiple gestation pregnancies with more than two fetuses are at a large risk of fetal and maternal complications that may threaten the survival of the mother or of one or more fetuses.[13–19] The

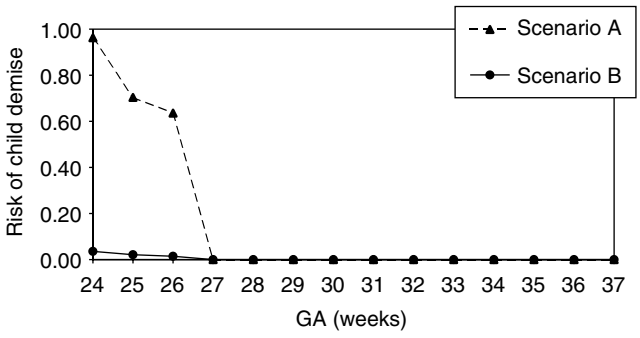

Figure 1. Comparison of the risk of dying for triplets born at a given gestational age in Scenario A versus the risk of dying for the remaining two fetuses born after that point in gestation in Scenario B.

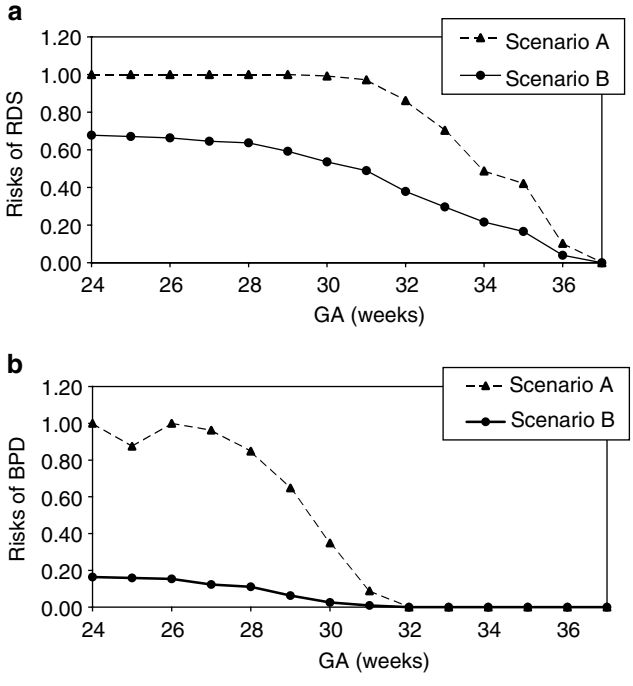

Figure 2. Comparison of the risk of developing pulmonary complications for triplets born at a given gestational age in Scenario A versus the risk of developing the same complications for the remaining two fetuses born after that point in gestation in Scenario B. (**a**) Risks of developing RDS. (**b**) Risks of developing BPD.

appropriate management of such gestations in each trimester has engendered significant controversy.[20–27] In this study, we have focused on one type of management issue, namely the approach to management when a single fetus is in jeopardy at or after 24 weeks gestation. The dilemma that the perinatologist faces is whether to effect an emergent delivery in the effort to ''rescue'' the jeopardized fetus but simultaneously place the two otherwise healthy fetuses at

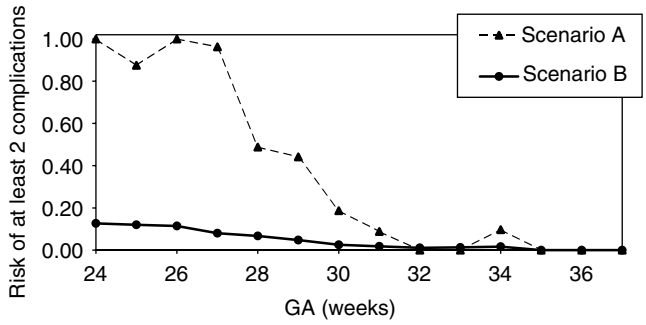

Figure 3. Comparison of the risk of developing at least two of the nonpulmonary complications (PDA, IVH, NEC, ROP or PVL) for triplets born at a given gestational age in Scenario A versus the risk of developing the same complications for the remaining two fetuses born after that point in gestation in Scenario B.

risk of complications of prematurity. Many caregivers approach this issue by defining an arbitrary gestational age below which interventions would not be attempted. Often this arbitrary age is significantly later than the threshold at which viability is considered likely.

As the number of triplet pregnancies has markedly increased, there has been an accompanying increase in the number of threatened triplet pregnancies.[1–4] As a result, there is a greater need for data that will help in determining appropriate interventions in such pregnancies. To our knowledge, this is the first study designed to investigate the risks to all products of a triplet pregnancy of developing neonatal complications based on intervention or nonintervention for a threatened fetus in the triplet cohort.

The decision of when it is appropriate in triplet gestation to intervene for a fetus in acute jeopardy must be based on many factors, including the relative risks of neonatal morbidity and mortality of the noncompromised fetuses. In this study, we compared the risks for triplet newborns assuming intervention and delivery at a given gestation, against the risk for the two surviving fetuses delivered after that point in gestation assuming that the jeopardized fetus was allowed to die in utero. Our model does not take into account two potential negative influences on the well-being of surviving fetuses. First, in this study we assumed that the outcome of one fetus is independent of the status of any of the other fetuses. However, some ART gestations are complicated by embryonic splitting resulting in monozygotic multiples.[28–31] Our analysis does not apply to such circumstances because the fetuses are no longer independent of one another. In monozygotic twin or higher order gestations, there is a risk of significant vascular connections between the monozygotic fetus(es). In the event of death of one of the fetuses, there is a significant risk of injury to the surviving fetus(es), presumably from hypotension as the survivor loses vascular volume into the

low resistance circulation of the dead fetus, and from the release of autolytic tissue factors from the dead fetus that reach the circulation of the survivor(s).[32–36] Thus, for our analysis to be useful, all reasonable steps must be taken to rule out monozygosity and vascular connections between the jeopardized fetus and one of the healthy fetuses through a careful ultrasound to evaluate for potential vascular connections. Second, it is possible that an intrauterine death in and of itself may create a hostile environment for surviving fetuses, but little is known about such possible risks. With these limitations in mind, this comparison showed that significant break points in risk occur between 26 and 31 weeks.

Many would argue that the most significant negative outcome of delivering at a very premature gestation age is neonatal mortality. Thus, the first focus of the study was on mortality differences between the two scenarios. We found that this was a significant consideration for both scenarios delivered prior to the 27th week. Infants delivered after this gestational age had a minimal risk for postnatal mortality in either scenario. However, the severely premature infants (24 to 27 weeks) differed considerably in regards to the neonatal mortality. For triplets born at 24 weeks, the neonatal mortality risk was greater than 95% (relative to scenario A). Yet, for the two remaining fetuses delivered at any point after 24 weeks, neonatal mortality risk decreased to less than 5% (relative to scenario B). The discrepancy in risk between the two scenarios might be partially explained by the fact that with the increase in the number of infants, there will be a concomitant increase in the risk of at least one neonatal death. The risk for one of the three fetuses dying is expectably greater than the risk of one of the two fetuses dying. However, even when this is accounted for, there was still a great difference between the two scenarios. Consequently, when solely considering neonatal mortality, these data do not support immediate delivery in the attempt to save the acutely jeopardized fetus prior to 26 weeks in gestation because of the significant additional risk of death.

After 26 completed weeks of gestation, morbidity became the primary risk factor for premature infants. For simplicity, the neonatal complications were broken down into two broad groups, those that included pulmonary complications and those that included nonpulmonary complications. Each of the pulmonary complications (RDS and BPD) was considered separately while all of the nonpulmonary complications (PDA, NEC, IVH, PVL and ROP) were considered together. The data on both pulmonary and non-pulmonary complications associated with premature delivery suggest that the significant reduction in the risk of developing complications occurs earlier for Scenario B than it does for Scenario A.

The complete data pointed strongly to the fact that if a triplet pregnancy were endangered by one jeopardized fetus before the 26th week, a delivery at that time would endanger all three infants with a high risk for infant mortality. After 26 weeks of gestation, there was no single best solution as to the best course of action. The decision should depend on the particular circumstances, including the risks that the physician and the family would be willing to take. However, these data do provide some guidelines as to the various risks and outcomes involved.

One important factor that our study does not address is the long-term outcome of the surviving infants. Many reports demonstrate important risks of both major and minor handicaps in surviving very low-birth-weight infants including survivors after fetal in utero death of a monozygotic twin.[11,12,14,36,37] We are unable to include this evaluation in our study because of a lack of a systematic follow-up evaluation program at our institution. However, the complications evaluated in this study are the ones that have a significant correlation to the risks of long-term handicaps. Thus, even in the absence of direct information on the long-term outcomes, our study provides useful insight into the potential impact of this important factor.

An additional consideration that this study cannot address is the possibility that the jeopardized fetus will have already experienced significant in utero damage,[25] which will not be reversed by the ''rescue'' effort, leading to either inevitable neonatal demise or inevitable long-term handicaps caused by PVL or other conditions. This question can only be addressed in a large population in which rescue was actively pursued, a condition which is not met by our population. Such an outcome, however, would likely serve to emphasize the differences between strategies obtained in this study.

Although these data do not provide physicians with exact dates for appropriate intervention in triplet pregnancies with a jeopardized fetus, they do provide useful information that will assist decision-making in such pregnancies. Further studies are needed to confirm these findings and to better establish the precise timing to be followed in such pregnancies.

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