Editorial: Does Intensive Perinatal Care Improve the Outcome of Extreme Prematurity? Addressing the Methodologic Issues

The value of obstetric and neonatal intensive care for treating extreme prematurity is a question of immense importance in perinatal medicine. Indeed, the potential benefits of intensive care—expressed in terms of the total years of life or total disability-free years that may be gained from such care—are likely to be greater in the perinatal period than at any other point in life. However, the potential costs—both human and financial—may also be greater, particularly for infants who survive with severe lifelong handicaps and for their families.

Considerable research will be required to determine the benefits, costs, and appropriate use of perinatal intensive care. In this issue of the Journal, Reuss and Gordon report a study conducted to relate fetal and neonatal survival in their institution to the decision whether to provide intensive obstetric care during labor. Such care included electronic fetal heart rate monitoring, administration of oxygen for signs of fetal distress, and, when necessary, Cesarean delivery for fetal distress as well as for abnormal presentation.

This study included 66 fetuses who were alive at the time of maternal admission, weighed between 500 and 749 g at birth, and were born in one perinatal center during 1984 and 1985 (excluding one infant with anencephaly). Fetuses whose estimated gestational age was 26 weeks or more or whose anticipated birthweight was 650 g or more (as assessed by sonography, menstrual history, and physical findings during pregnancy) during labor were considered to be viable. Based on this assessment, a decision involving the perinatologist, the neonatologist, and the parents was made either to administer or forego intensive care. In the analysis, the patients were categorized according to this treatment plan. The investigators refer to the two groups as either "considered viable" (n = 43) or "considered nonviable" (n = 23). However, because the treatment plan did not always correspond to the viability assessment and because maternal complications and risks as well as fetal viability were undoubtedly considered, the groups might have been better labeled as "intensive care considered to be indicated" or "intensive care considered to be not indicated."

Of the 23 fetuses considered nonviable, 5 (22%) died; however, only 1 of 43 (2%) fetuses considered viable died (P < 0.02). Only 1 of 23 (4%) fetuses considered nonviable survived to nursery discharge; in contrast, 19 of 43 (44%) fetuses considered viable survived (P < .01). As intended, the median birthweight and gestational age were greater (by 100 g and 3 weeks) for infants considered viable than for those considered nonviable. However, survival was more closely related to the treatment plan than to birthweight and gestational age. In logistic regression models adjusting for birthweight, gestational age, vertex presentation, chorioamnionitis, and Cesarean delivery, the odds ratio for perinatal survival to nursery discharge was 17.6 for infants considered viable compared with those considered nonviable. The investigators note that similar results were obtained regardless of the combination and

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Editor's Note. See related article by Reuss and Gordon (p 362) in this issue.
order of the potential confounders entered into the logistic regression model.

The study's strengths include the willingness of the clinicians to expose highly sensitive decisions to scrutiny, systematic documentation of the treatment plan in the maternal chart, collection of obstetric data by evaluators blinded to the neonatal chart, and evaluation of the treatment plan with an intention-to-treat analysis. The investigators take care to acknowledge the study's limitations, including the need to study a more recently treated population and to assess a larger sample of patients. With the sample size studied, the effect of decisions about obstetric intensive care could not be precisely estimated, a problem apparent in the wide 95% confidence intervals (1.77, 175) around the odds ratio of 17.6 for perinatal survival among fetuses considered viable. As Chalmers and Sinclair showed, statistically significant results in small studies tend to overestimate treatment effect. Reuss and Gordon identified no significant effect of birthweight and gestational age on perinatal survival after adjusting for the treatment plan during labor. Such a finding suggests that part of the effect attributed to the treatment plan may have been due to birthweight or gestational age. Because the treatment plan was based largely on gestational age and anticipated birthweight, it may be difficult to sort out the independent effects of these factors. Fetal sex—a factor known to affect perinatal outcome—was not included in the regression equations and might also have contributed to the findings.

Aspects of care before the labor that resulted in delivery were not addressed in the study. Moreover, advances in perinatal care since the study period, including increased use of maternal steroid administration and the introduction and widespread use of neonatal surfactant therapy, make it important to study contemporary populations to define the value of aggressive care before, during, and after extremely premature labor.

Nevertheless, Reuss and Gordon make an important point: the difference in outcome often attributed to birthweight or gestational age may be heavily influenced by gestational-age-dependent or birthweight-dependent differences in perinatal care. Recent advances in care are likely to increase the importance of decisions to use perinatal intensive care.

Decisions about obstetric intensive care may influence outcome in a variety of ways. Two of the deaths among fetuses considered nonviable in the study followed prostaglandin induction of labor. Parly for this reason, the greater survival in the group considered viable might be due less to intensive obstetric care than simply to the kind of observation and supportive care routinely used during labor at term. The benefits of some components of intensive obstetric care (e.g., electronic fetal heart rate monitoring) are disputed, even for high-risk pregnancies. Moreover, as Reuss and Gordon document, decisions to use intensive obstetric care are likely to increase the intensity of neonatal care. The greater use of endotracheal intubation for infants considered viable than for those considered nonviable may well have been accompanied by greater expertise of the neonatal staff present at birth and greater use of mechanical ventilation in the neonatal intensive care unit. Thus, a variety of factors only indirectly related to the aggressive methods of obstetric care during labor may have influenced outcome.

Reuss and Gordon prudently refrain from using their findings to recommend greater use of intensive obstetric and neonatal care in cases of extreme prematurity. Partly because perinatal intensive care may reduce resources available for other purposes valued by society and partly because it may increase the morbidity of mothers and the suffering of newborns who die, such care is not necessarily justified simply because survival is somewhat increased. Elsewhere, I discuss my views on the complex ethical issues and the ethical criteria that should be used to define when neonatal intensive care should be considered mandatory, optional, investigational, or unreasonable.

With respect to the methodologic issues, what should be done to define more rigorously the proper use of intensive care for marginally viable fetuses and newborns? At least in the United States, randomized trials of perinatal intensive care are unlikely to be accepted by parents and clinicians, even if their ethical basis were accepted by institutional review boards and funding agencies. The most rigorous design feasible may be that of a "preference trial," in which therapy is assigned within a defined cohort of patients according to the treatment choices selected by informed parents and physicians. (Such a design could be used to evaluate newborn intensive care alone or obstetric intensive care with the accompanying level of neonatal care.) In assessing obstetric intensive care, it would be important to assess pregnancy outcome for a cohort of women for whom decisions were made either to initiate or forego aggressive antepartum or intrapartum care for the extremely premature fetus (perhaps at 21–25 weeks gestation). Because such care may influence the time of delivery, outcome should be compared for all fetuses in the two groups irrespective of the birthweight or gestational age at delivery. Ideally, the outcomes assessed would include total life-years gained from use of perinatal intensive care, the quality of life of the surviving children and of the family, the subsequent number of children born to the mother, and the long-term resource costs and gains associated with handicapped and nonhandicapped survivors.

Such a study involves daunting practical and methodologic problems. Large geographically defined populations free of referral biases should be studied. The appropriate ways to involve parents in decision making and to measure quality of life are difficult issues. Current follow-up programs are poorly funded and have not involved families of infants who died, a group that is crucial in assessing the effects of decisions to forego intensive care. Moreover, the problems in identifying and adjusting for potential confounders in preference trials should not be underestimated. It would be difficult, for example, to adjust for parental socioeconomic variables likely to influence both perinatal decision making and long-term outcome for surviving infants. Finally, even the short-term medical costs are difficult to measure, in part because hospital accounting systems in the United States were developed to facilitate revenue collection and cannot be assumed to reflect true resource costs.

Nevertheless, considerable progress has been made in developing methods to address these problems. The issue of parental involvement in perinatal treatment decisions is receiving increasing attention. Interactive videodiscs similar to those said to facilitate patient involvement in major treatment decisions in other fields of medicine might be developed and tested as a means to better involve parents in decisions about perinatal intensive care. The outcome for extremely low birthweight infants has been recently described in a number of large neonatal and follow-up studies. Saigal and coworkers recently reported an important controlled study of the health-related quality of life at 8 years of age in a geographically defined cohort of ex-
tremely low birthweight children. Utilities were used to estimate a single value between 0.0 and 1.0 (0 = dead; 1 = perfect health) to reflect the global health-related quality of life for individual children.

Utility scores may be used in assessing the proportion of children whose health-related quality of life is considered worse than death from the perspective of the parents or that of society in general. Saigal is now assessing quality of life in this cohort from the perspective of the children themselves as teenagers.

A comprehensive economic evaluation of neonatal intensive care was done by Boyle and colleagues in Canada. This study, reported 12 years ago, needs to be repeated. The feasibility of such a study in the United States is enhanced by ongoing changes in health care reimbursement that provide incentives to health care institutions to determine the true costs of expensive methods of care. My colleagues and I have quantified the resource costs in terms of the number of additional days of intensive care required per survivor (or the number required per survivor without major neonatal morbidity) in different risk groups among infants with birthweights of 501 through 800 g. Viability, major morbidity, and resource requirements among newborns 501–800 g birth weight. Submitted for publication.

Although impairment rates of 30% to 40% have been reported in some recent studies of extremely small or preterm infants, only a small proportion of school-age survivors have the kind of devastating problems that most parents are likely to consider worse than death. Moreover, the costs of neonatal intensive care—if expressed per life-year gained or per quality-adjusted life-year gained—are likely to be less than those for intensive care of many older children and adults (Tyson et al., submitted manuscript).

Although these findings seem encouraging, the benefits and hazards as well as the cost-effectiveness of perinatal intensive care relative to other expensive methods of treatment need much more study. Whether or not to administer perinatal intensive care at the margins of viability continues to be an extremely difficult decision that should be based on the best information possible. High priority should be given to developing and implementing improved methods to address the long-term effects of decisions to use perinatal intensive care.

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References

Editorial: Can We “Cure” Mild Mental Retardation among Individuals in the Lower Socioeconomic Stratum?

In 1962, the President’s Panel on Mental Retardation suggested that the use of existing knowledge could “eliminate perhaps half or more of all new cases of mental retardation.” The possibility of increasing intelligence quotients gained popularity in the ensuing decade, fueled by a naive belief in the unlimited power of the environment to shape human traits. By 1972 the panel, now called the President’s Committee on Mental Retardation, reiterated its suggestion with the strength of a declaration: “Using present knowledge ... it is possible to reduce the occurrence of mental retardation by 50 percent before the end of this century.” President Richard Nixon proclaimed this to be a major national goal, sparking interest in research and intervention activities. As the millennium draws near, it seems appropriate to assess the progress that has been made toward