A Review of Ethical Issues Involved in Premature Birth

Gerri R. Baer and Robert M. Nelson

Morning rounds on any day in any academic neonatal intensive care unit (NICU) are likely to involve some reference to an ethical dilemma. Many ethical questions have been defined in the area of premature birth, and many more will arise. Advances in medical technology have allowed neonatologists to provide premature infants mechanical ventilation, intravenous nutrition, and artificial surfactant, but prevention of major complications of prematurity remains elusive. It also appears that a threshold of viability has been reached, before which neonatal technology is of no benefit.

In this paper, we provide a review of the literature describing ethical issues related to premature birth. We focused our initial literature searches on empirical studies and added judicial decisions, commentaries, and ethical analyses to complement the data. There are many ethical issues related to prematurity for which there are no empirical data, and we have commented accordingly.

We first present the literature on decision making, which is one of the most frequently addressed areas in neonatal ethics. We discuss the two main frameworks for decision making in the neonatal period, describe several high-profile court cases, and present the difficulties with achieving informed consent. Next, we review approaches to conflicts between the autonomy of the pregnant woman and her obligations of beneficence toward the fetus. We then present the current attitudes and practices with respect to the limits of viability.

Next, we present the literature related to ethical issues in end-of-life care, including the practice of withholding or withdrawing life-sustaining medical treatments, pain control and palliative care, the concept of futility, and the differences in end-of-life practices between U.S. physicians and physicians in some parts of Europe. We then examine the literature concerning the economic and social implications of premature birth. Finally, we comment on the inclusion of pregnant women, fetuses, and neonates in research.

ETHICAL ASPECTS OF DECISION MAKING

The predominant ethical paradigm for decision making about the early stages of reproduction (i.e., preventing pregnancy, becoming pregnant, deciding to stay pregnant, and engaging in activities that may help or harm a fetus) focuses on the autonomy of the woman. A transition occurs in midpregnancy, wherein the emphasis on a woman’s autonomy is weakened in favor of balancing fetal and maternal “best interests.” For some, this shift may be viewed as occurring when either the choice or the opportunity for termination of the pregnancy has passed. This time of transition during pregnancy from a previable to a viable fetus (i.e., 23 to 25 weeks of gestation) can also be viewed as an ethical (and perhaps legal) transition from an individual autonomy-based model of decision making to a negotiated beneficence-based model of decision making. This view, although useful, is perhaps an oversimplification, as fetal interests are often important factors early in pregnancy and maternal autonomy remains influential during the late stages of pregnancy.

The paradigm (in the United States and most Western countries) for proxy decision making for infants and children focuses on a child’s “best interest,” with the parents or guardians generally viewed as the primary surrogate decision makers for their infants. However, health care professionals play an important role in determining what actions are, in fact, in a child’s best interest, leading to a more complex “negotiated” decision-making process. Ethical dilemmas may arise when parents and the medical professionals caring for their infants disagree on the best course of action.

Empirical Data Concerning Proxy Decision Making
Parents largely believe that they do and should take primary responsibility for decisions concerning the limitation or withdrawal of life-sustaining medical treatment (LSMT) from their critically ill infants. The majority of health care professionals believe that parents should not be solely responsible, but also that physicians often make the “final” decision in actuality. The dramatic difference in perceptions may reflect a complex process of shared decision making by use of a “negotiated” model of best interest. We first present data on parental perceptions, followed by data on health care professionals’ perceptions and studies that have combined both groups. Most of the following data were collected outside the United States and thus may not reflect the attitudes of families and the practices of physicians in the United States.

Semistructured interviews of parents of infants in NICUs were performed in Scotland by a research team led by Hazel McHaffie. Parents were interviewed about whether any discussion of limitation of their infants’ LSMT had occurred. The interviews revealed that 56 percent of the parents thought that they had taken the responsibility for decision making, with three-quarters of those believing that it had been their decision alone and one-quarter believing that the decision had been made in conjunction with the infant’s doctors. Eighty-three percent of parents believed that the correct person(s) had made the decision. The authors concluded that parents desire involvement in decision making (1).

An international study group interviewed the parents of surviving very low birth weight (VLBW) infants to examine their perceptions of perinatal counseling and decision making at nine centers in Pacific Rim countries and two centers in San Francisco, California. The majority of subjects were the parents of survivors, as cultural taboos prevented interviewing the parents of deceased infants in most countries. In all countries, more than 90 percent of the parents believed that the physician’s opinion was important in decisions regarding resuscitation status. A large majority of the parents in all countries (93 to 100 percent) considered the physician’s opinion in decisions regarding resuscitation status. In all locations except Melbourne, Australia, the majority of parents (75 to 86 percent) perceived that there was joint decision making between the physician and the parents. In Melbourne, three-quarters of the parents perceived that the physician made the decision alone. A majority of parents at all sites (62 to 95 percent) preferred the model of joint decision making. In the assessment of antenatal counseling, a majority of the parents at all centers (65 to 90 percent) believed that they understood their infant’s prognosis after antenatal counseling. More than three-quarters of all parents thought that the sequelae of their infants’ illnesses were better than they had expected. The authors concluded that parents across the Australasian countries make decisions similarly, with importance placed on physician and partner input. They also concluded that parents prefer a joint decision-making approach and believe that it often happens. Finally, parental assessment of the adequacy of antenatal counseling was found to differ by center and by topic (2).

In contrast to many studies showing parental preference for joint decision making, a qualitative interview study from Norway revealed that most parents believed that the physician should be the one to make the final decision on an “end-of-life” question but that the decision should be made with parental involvement. Families emphasized health care professionals’ experience and knowledge, the parents’ incapability to make a rational decision, and the parents’ need to be taken seriously and listened to (3).

The Scottish research team also performed surveys of health care professionals concerning decision making in the NICU. Analysis of those data revealed that only 3 percent of physicians and 6 percent of nurses believe that parents should make the ultimate decision to withhold or withdraw LSMT. Rather, parents should be involved but should not be solely responsible for decision making (4).

A recent survey of New England neonatologists sought to describe current practices of delivery room decision making and prenatal consultation at the border of viability. Given a hypothetical scenario of impending delivery of a 23.5- to 24.5-week preterm infant of appropriate weight for gestational age, more than three-quarters of neonatologists believed that they and the parents should make the final decision together. However, only 40 percent of the neonatologists believed that both parties actually made the final decision. Half the neonatologists reported that they made these decisions alone, in reality. Regarding their role in perinatal consultations with parents, 58 percent of the neonatologists believed that their
primary role in discussing resuscitation strategies with parents was providing factual information, in contrast to the 40 percent who believed that their primary role was assisting the parents in weighing the risks and the benefits of their resuscitation options. Predictors of shared decision making were believing that the primary role of the neonatologist was to assist parents in weighing their options (odds ratio [OR] = 4.1, p = 0.004) and being in practice >10 years (OR = 3.6, p = 0.004). The authors concluded that neonatologists should continue to incorporate parental preferences and should improve communication about long-term outcomes and quality-of-life issues with families to comply with American Academy of Pediatrics (AAP) recommendations on perinatal consultation (5).

In a Canadian survey of parents of extremely low birth weight (ELBW) survivors, neonatologists, and neonatal nurses, nearly all parents and more than three-quarters of the health care professionals either agreed or strongly agreed that the parents should have the final word regarding the initiation or the limitation of treatment. In contradiction to that finding, the health care professionals also agreed or strongly agreed nearly 100 percent of the time that doctors should make the final decision. Parents agreed or strongly agreed 50 to 75 percent of the time that doctors should make the final decision. The authors concluded that the physicians polled believed that they should have more of a role in decision making than the parents wanted to allow them (6).

A comparative case-based qualitative study of decision making was conducted in NICUs in both France and the United States. Over a 2-year period, the investigators interviewed 60 clinicians and 71 parents, as well as conducted a chart review of end-of-life cases. The investigators concluded that the autonomy that parents are thought to have in the United States is not true autonomy, citing findings that the clinicians decide when to broach issues and decision points, that withdrawal is offered only on severely moribund infants who are certain to die, and that neonatologists do not ask parents’ permission to continue treatment; rather, they ask parents’ permission only to discontinue treatment (7).

The “Best Interests” Standard and Decision Making

The model of collaborative decision making is endorsed by numerous sets of professional guidelines. Many authors have acknowledged that although a collaborative model with emphasis on parental autonomy and values is ideal, it remains difficult to achieve. There is an imbalance of knowledge, control, and expertise in favor of medical professionals, who at times may have a different assessment of an infant’s “best interest.”

In her commentary on decision making and parental autonomy, McHaffie made the case that parental autonomy was impossible. She argued that (a) physicians may present facts along with guidance toward the recommended medical option; (b) an imbalance of power exists between parent and physician; (c) parents rely on the medical team for facts, and the physician may include or exclude information in an effort to persuade the parents to choose his or her professional recommendation; and (d) physicians may not offer certain options unless they are convinced that the options were the appropriate course of treatment, thus weighting the balance of power in the relationship toward the physician (4).

A group of prominent North American neonatologists, pediatricians, and intensive care physicians convened to review questions regarding decision making at the end of life in ELBW infants. The results of their discussions were published in 1994. Questions were asked regarding the withdrawal of a burdensome treatment in several cases of infants with chronic disease. These physicians concluded that “parents, in consultation with a physician who has provided ongoing care to the child, are in the best position to make the difficult decision to discontinue support.” These discussions also shed light on ethical dilemmas, such as the fact that parents’ options for withdrawing life-sustaining treatments are subject to their “physicians’ practice styles and moral values.” The group concluded that “physicians should be careful to separate their personal views … from current medical, legal, and moral standards of care for such children” (8).
The AAP Committee on Fetus and Newborn published guidelines in *The Initiation or Withdrawal of Treatment for High-Risk Newborns* and recommended an active role for parents in decision making. However, they state, “physicians should not be forced to undertreat or overtreat an infant if, in their best medical judgment, the treatment is not in compliance with the standard of care for that infant” (9).

Leuthner, in a commentary on the four AAP policy statements related to decision making for premature and/or critically ill newborns, argued that the most appropriate model of “best interest” is a “negotiated” model. That model strongly incorporates parental values as well as the objective medical facts and acknowledges that the moral values of the physician should be respected (10).

Loretta Kopelman, a bioethicist who has written extensively about ethical issues in prematurity, recently proposed a negative version of the Best Interests Standard, which applies to incompetent individuals of all ages and (1) instructs decision makers to decide what act(s) [is] in the incompetent individual’s immediate and long-term interests and maximize his or her net benefits and minimize net burdens, setting that act(s) as a prima facie duty; (2) presupposes a consensus among reasonable and informed persons of good will about what choices for the incompetent individual are, all things considered, not unacceptable; and (3) determines the scope of the Best Interests Standard in terms of the scope of established moral or legal duties to incompetent individuals” (11).

She defended this version of “best interests,” as it allows parents to make choices within ranges of options that are acceptable to “reasonable and informed people of good will and fulfill basic duties.” Use of this standard “requires what is reasonable” and “makes room for individualized and compassionate choices that may reflect somewhat different values” (11).

**Parental Informed Consent: Legal Precedents**

Ethically, physicians have a duty to inform the parents and potential parents of newborns about resuscitation procedures and potential outcomes for their preterm infants as well as to obtain their consent (either implicit or explicit) to proceed with resuscitation and treatment. The process of informing is inherently flawed by the uncertainty of predicting outcomes and is often flawed by the urgency and tension of the potential parents’ situation. The question of whether physicians require parental consent to resuscitate premature infants has been addressed in several high-profile court cases.

Although the 1994 *State v. Messenger* case in Michigan supported the right of a parent to refuse LSMT for a 25-week-gestation infant, the more recent *Miller v. HCA* (Texas, 2003) and *Montalvo* (Wisconsin, 2002) cases have restricted the parents’ role in resuscitation decisions of an ELBW infant. The *Miller* case held that a physician was not bound by the prior expressed wishes of the parent since the infant could not be evaluated prior to birth. Although the *Miller* infant was resuscitated, the court decision does not compel resuscitation of ELBW infants but allows for professional judgment about “warranted medical treatment.”

*State v. Messenger* (1994) in Michigan affirmed the right of an infant’s father to refuse treatment for his child who was born at 25 weeks of gestation. The *Messenger* infant was resuscitated against the expressed wishes of his parents. Once in the NICU, the infant’s father, a physician, asked to be alone with his son and disconnected the ventilator so that the infant would expire. Dr. Messenger was charged with manslaughter and tried in a criminal court, where he was acquitted by a jury (12).

The problem of achieving informed consent for resuscitation of premature infants was brought to public attention by the case of *Miller v. HCA* (which was decided in 2003). Sidney Miller was born in 1990, at 23 weeks of gestation and with a body weight of 615 grams. Prior to delivery, the Miller parents had told their obstetrician and the neonatologist that they wanted no heroic measures performed to resuscitate the infant. A hospital administrator incorrectly informed the medical team that the hospital had a policy of
resuscitating every infant born weighing at least 500 grams. The neonatologist at the delivery noted that the infant had a heartbeat and cried spontaneously, so he intubated her and began artificial ventilation. At several days of life, Sidney suffered a brain hemorrhage and now lives severely mentally and physically impaired. The Millers sued the hospital for battery and negligence for treating the infant without consent. Initially, the family was awarded $60 million by a jury, but the judgment was overturned by the Texas Court of Appeals. Citing the Texas Natural Death Act, the court ruled that parents could withhold treatment only if their child’s medical condition was terminal. In the subsequent appeal to the Texas Supreme Court, it was decided that parental consent was not required for resuscitation, during the “emergent circumstances” of preterm birth. “Sidney could only be properly evaluated when she was born. Any decision … made before Sidney’s birth … would necessarily be based on speculation.” Although “best practice is to obtain parental consent before birth to make an evaluation and render ‘warranted medical treatment,’” the Court declined “to impose liability [for battery or negligence] … solely for providing life-sustaining treatment under emergent circumstances to a new-born infant without that consent” (13).

It should be noted that the absence of a parental right to refuse resuscitation does not imply that a physician is obligated to resuscitate. A physician should still make a professional judgment as to whether resuscitation is medically warranted.

**Empirical Data Regarding Informed Consent**

Concerns about the challenge of obtaining informed consent for neonatal resuscitation are reinforced by evidence that health care professionals incorrectly estimate survival and disability rates for ELBW infants. Achieving informed consent for procedures and research may also be problematic. One study has shown that parents have difficulty recalling crucial content communicated during the consent process for research. Underestimating survival of preterm infants may also lead to inappropriate obstetrical decision making.

The difficulty in ensuring accurate prenatal counseling was demonstrated in a study from Vermont, which tested health care professionals’ estimates of survival before and after an intervention to educate them on current survival data. Obstetricians, neonatologists, nurses, and nurse practitioners were found to underestimate survival rates and overestimate major disability rates for premature infants at various gestational ages. Physicians and nurses underestimated the rates of survival at 23 to 28 weeks gestation, and nurse practitioners underestimated the rates of survival at 23 to 27 weeks gestation. For example, physicians’ mean estimate of the rate of survival at 25 weeks gestation (prior to the study intervention) was ~50 percent, although the actual survival rate was closer to 75 percent. Physicians and nurses overestimated disability rates at <26 weeks of gestation, and nurse practitioners overestimated disability rates at <28 weeks gestation. For example, nurse practitioners’ mean estimate of major disability at 25 weeks gestation was ~65 percent, whereas the actual disability rate was ~30 percent. The inaccuracy of health professionals’ estimations of survival and disability rates decreased after an educational intervention, but the inaccuracies did not completely disappear. The authors concluded that improved education of health care professionals is needed to ensure accurate counseling for families (14).

Obstetricians and family practice physicians who performed deliveries were surveyed in Alabama in 1992 regarding the perceived rates of survival and obstetric practices between 23 and 36 weeks gestation. The respondents significantly underestimated the rates of survival and freedom from handicap for all gestational ages. The respondents reported that they would transfer pregnant women to a perinatal center for management at a mean of 23 weeks gestation, and most would administer steroids for fetal lung maturity at a median earliest gestational age of 25 weeks. However, only half of the respondents would have performed a delivery by cesarean section for fetal distress at 25 weeks gestation, which raised concerns for the authors that underestimation of the rates of survival and survival free of handicap was leading to inappropriate obstetric care. When compared with the authors’ study that estimated rates of survival and that had been conducted 10 years earlier, estimates of survival had improved, but perinatal management had not changed adequately to reflect the improved rates of survival (15).
The validity of informed consent obtained in the neonatal period was examined by Ballard et al. In telephone or face-to-face interviews of parents who had consented to enroll their neonates in the NEOPAIN trial, the investigators found that 8 percent of parents had no recollection of the study at all. Of the parents who recalled the study, about two-thirds recalled the purpose of the study. Ninety-five percent of parents who recalled that their infants had entered the study could verbalize potential benefits, but only 5 percent could recall one or more risks. The time interval between the time that they signed the consent and the study interviews did not affect understanding of the NEOPAIN study’s purpose, risks, benefits, or voluntary nature. Mothers were more likely than fathers to recall the purpose and benefits of the study, and administration of magnesium sulfate had no effect on the mother’s recall. When stringent criteria of informed consent were used (understanding of the purpose, benefits, and risks of the study; understanding the voluntary nature of the study; and freedom from coercion), only 3 percent of the parents met the criteria for giving informed consent. The authors were concerned that the provision of informed consent by parents of ill neonates is not achievable in the current model. They suggested modifications to the process, including emphasis of the presence of risks and an interactive consent process that includes plenty of time for the parents to ask questions (16).

ETHICAL TENSIONS DURING PREGNANCY: BALANCING THE INTERESTS OF THE PREGNANT WOMAN AND HER FETUS

Over the past 2 to 3 decades, multiple paradigms have been proposed for the discussion and resolution of so-called maternal-fetal conflicts. Some authors have proposed that maternal autonomy should be the dominant concern in decision making, whereas others have established the fetus as a patient who should be treated according to the principles of beneficence. A number of cases of court-ordered interventions for pregnant women have received publicity, but these cases are rare. The tension between maternal autonomy and fetal best interest may be seen in decisions about the mode and the location of delivery. For example, a pregnant woman may decide against delivery by cesarean section in the case of fetal distress, yet ask that all resuscitative measures be used after delivery.

In the past 20 years, Chervenak, an obstetrician-gynecologist, and McCullough, an ethicist, have written extensively on the approach to maternal-fetal conflicts. They start with the concept of the fetus as a patient. They do not argue that the fetus is a person with the rights of personhood but argue that the fetus is a patient who should be managed according to beneficence principles. In an often-cited paper from 1985, they defined the ethical obligations of the parties involved in ethical conflict as the maternal autonomy-based obligations of the physician, the maternal beneficence-based obligations of the physician, the fetal beneficence-based obligations of the mother, and the fetal beneficence-based obligations of the physician. When maternal autonomy and fetal beneficence came into conflict, they recommended persuasion of the pregnant woman to undergo treatment to benefit the fetus and stated that coercion or court intervention may sometimes be justifiable on a moral basis (17). In 1993 they published “An Ethical Justification for Emergency, Coerced Cesarean Delivery,” which allowed coerced delivery by cesarean section if the procedure was likely to prevent morbidity or mortality to the infant, there was no physical resistance from the woman, and there was no time to obtain a court order (18).

In 1990, the American Medical Association suggested guidelines for consideration of justifiable court-ordered interventions for pregnant women, including stipulations that the intervention must pose minimal risk to the woman’s health, involve minimal invasion of her bodily integrity, and have a high probability of preventing substantial, irreversible fetal harm (19).

The American College of Obstetricians and Gynecologists (ACOG) has published several statements on the matter of coerced or court-ordered intervention during pregnancy. In 2004, ACOG published an ethics handbook that stated that in cases of maternal refusal of treatment, intervention by courts against the pregnant woman’s wishes is “rarely if ever acceptable.” The paper recommended examining the barriers to health-promoting behavior, addressing the social and cultural contexts of the woman’s decisions, and recognizing the fallibility of medical knowledge (20).
In 2005 ACOG published a committee opinion, “Maternal Decision Making, Ethics, and the Law.” In the opinion, the Committee on Ethics strongly opposes coercive and punitive legal approaches to pregnant women. The committee argued that (a) coercive and punitive actions violate the entitlement of competent adults to informed consent, (b) court orders for intervention neglect the fact that there are limitations to medical knowledge and prediction of outcomes, (c) coercive and punitive policies have a detrimental effect on prenatal care and the physician-patient relationship, (d) “coercive and punitive policies unjustly single out the most vulnerable women,” and (e) these policies create the potential to criminalize otherwise legal behavior by pregnant women. The committee recommended that “in the absence of extraordinary circumstances … judicial authority should not be used to implement treatment regimens … for such actions violate the pregnant woman’s autonomy” (21).

Lisa Harris, in an essay in Obstetrics and Gynecology, proposed new methods for framing and solving maternal-fetal conflicts. Framing maternal-fetal conflict as the “conflict between clinicians’ moral obligations, not maternal and fetal rights,” has worked best in the obstetrics literature, and Harris defined the ethical dilemmas in this way. She argued that the limitations of using principles to frame these dilemmas are that the principles are “difficult to use when negotiating moral dilemmas between intimates”; that life particularities, such as social class, race, politics, and religion, must also be considered when judging ethical dilemmas; and that principle-based ethics “neglects the broad social and political arrangements in which clinical care occurs,” citing difficulties with the hierarchy of power that exists between physician and patient, particularly in cases of sex, race, and class inequality. Finally, she suggested that an alternative model for addressing perinatal ethical dilemmas would include attention to understanding the pregnant woman within the context of her social network and community, addressing the clinicians’ standpoint and ethical judgment, and recognizing that the generation of a diversity of opinions may help to deal with issues of race and sex inequalities (22).

Brain Death in Pregnant Women with Periviable Fetuses

Although brain death in pregnant women with periviable fetuses has been and continues to be of interest to the media (and some ethicists), it is of little ethical value in illuminating decisions about premature infants. The pregnant woman who is now dead has no “interests” (other than perhaps the respectful disposition of her body, although the principle of “respect for the dead” is grounded in the moral obligations of the living rather than a right of the once living who survives death), and thus, there is no conflict between the now-dead pregnant woman and the still living fetus. These cases usually reflect conflict within the family or confusion about “brain death” (as in the headline “Brain Dead Pregnant Woman Dies”).

Veatch defined the two potential ways to view these cases as (a) the pregnant woman is alive but terminally ill; therefore, continued treatment would be appropriate; or (b) the pregnant woman is newly dead, in which case the legal and ethical justifications for continued support are more difficult; but with no argument among family members, the life of the brain dead pregnant woman might be maintained if the fetus is near viability. Decisions under these circumstances hinge on states’ definition of death and any prior expressed wishes of the now-dead pregnant woman and/or her surrogate decision makers (23).

In a review of 10 cases of extended somatic support for pregnant women who had suffered brain death, it was reported that all 10 infants survived. They were born between 26 and 33 weeks of gestation, and of the six infants for whom follow-up information was available, none was developmentally delayed. A review such as this is subject to publication bias, as no cases of adverse neonatal outcomes in this setting were reported in the literature. The authors briefly raise some ethical questions inherent in providing somatic support for pregnant women, including the question of when and if the fetus becomes a patient and who should be the surrogate decision maker(s) for the mother and the fetus (24).

Decision Making in Situations of Maternal Illness
There are no general obstetric guidelines regarding when preterm delivery is indicated. However, in specific instances of maternal illness, preterm delivery may be required to restore the mother’s health. ACOG guidelines for the treatment of preeclampsia state that the diagnosis of severe preeclampsia “usually warrants delivery.” Immediate delivery is also the standard of care for pregnant women who have developed HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count) or who have eclampsia (25).

Intrauterine Intervention and Maternal-Fetal Surgery

The development of fetal treatments, including surgery, has contributed to conflicts of maternal and fetal best interests by offering interventions that are intended to benefit the fetus while placing the pregnant woman at some degree of risk. Some authors have promoted calling these interventions “maternal-fetal surgery” to acknowledge the intervention to both the pregnant woman and the fetus (26). The importance of informed consent becomes paramount in the decision-making process prior to intervention. Given the need to place the pregnant woman at risk during a fetal intervention, the evidence for the effectiveness of the intervention must be compelling and the risk to the pregnant woman must be negligible to warrant an attempt to compel fetal treatment over maternal objections. To date, there have been no published empirical studies to examine the ethics of fetal surgery.

Professional Guidelines and Ethical Commentary on Fetal Intervention

The AAP Committee on Bioethics published “Fetal Therapy—Ethical Considerations” in 1999. This statement acknowledges the ethical issues inherent in fetal therapies as they relate to the best interests of both the fetus and the pregnant woman. The committee advises a multidisciplinary collaborative approach to directly communicate with the pregnant woman and her partner about all the risks and benefits of fetal therapies. It also emphasizes that procedures of unproven efficacy should be undertaken only as research, with appropriate voluntary informed consent. To consider opposing a woman’s refusal of intervention, the following criteria must be met: “1) there is reasonable certainty that the fetus will suffer irrevocable and substantial harm without the intervention, 2) the intervention has been shown to be effective, and 3) the risk to the health and well-being of the pregnant woman is negligible” (27).

In an analysis of the ethical issues relevant to maternal-fetal surgery, a group of bioethicists and obstetricians reviewed current practices and made recommendations for the scientifically and ethically sound practice of maternal-fetal surgery. They raised the following ethical issues: the risks and benefits to the pregnant woman, problems obtaining informed consent (i.e. “therapeutic misconception”), concerns about the ethics of intervention for nonlethal conditions, withholding intervention for those not in a randomized trial, concerns about entrepreneurship, and prioritization for funding. The group’s recommendations included: “1) innovation in maternal-fetal surgery should be conducted and evaluated as research, 2) women must be considered research subjects …, 3) the informed consent process must ensure adequate comprehension and genuine voluntariness …, 6) centers of excellence should be established for conducting research and providing maternal-fetal surgery, [and] 7) funding for research on maternal-fetal surgery should be considered in the context of societal needs” (26).

Chervenak and McCullough have proposed an ethical framework for consideration of initiating research in fetal surgery. Their framework is based on the concept of the viable fetus as a patient and the nonviable fetus as a patient if it is conferred that status by the pregnant woman. Their criteria for preliminary investigation state that (a) the intervention must either be life saving or prevent serious and irreversible disease or handicap; (b) the intervention must minimize risk and morbidity to the fetus; and (c) the intervention must pose a low risk of death to the pregnant woman and a low or manageable risk of disease, injury, or handicap. They further state that investigators have an ethical obligation to protect potential subjects from “unreasonably risky research” and consider “beneficence-based, risk-benefit analyses.” The authors also emphasize the importance of “rigorously nondirective” counseling and voluntariness in consent (28).
Infertility Treatments and Ethical Conflict

There has been increasing recognition of the tension between maternal autonomy (for example, transferring multiple embryos to achieve at least one viable pregnancy) and fetal interests (for example, the risks associated with multiple fetuses). Selective reduction has not been a solution, as often couples opting for assisted reproductive technologies (ART) are also opposed to termination, even if a reduction in the number of fetuses is in the collective interest of the remaining fetuses. There is some concern that even singleton infants conceived by the use of ART procedures may have worse perinatal outcomes. If one assumes that this is true, then the decision to use ART may be thought of as a moral decision, balancing the desire of the parents to have children and the risks to their potential children. No published empirical research to date has specifically examined the ethics of ART.

ACOG recently issued a committee opinion, “Perinatal Risks Associated with Assisted Reproductive Technology.” The report acknowledges data that have shown poorer birth outcomes in all infants conceived by the use of ARTs, including higher rates of perinatal mortality and higher incidences of prematurity, low birth weight, and small-for-gestational-age status. They recognize that measurement of these outcomes may be confounded by the etiologies for the infertility itself. The authors also describe an overall 30-fold increase in multiple pregnancies, although the rate of high-order multiples declined between 1998 and 2001. Recommendations for decreasing the rate of high-order multiples include preconception counseling about the option of multifetal pregnancy reduction and limiting the number of embryos transferred (29).

Several studies have shown that more preterm or low birth weight (LBW) infants are born to parents who conceived by the use of ARTs than to those who conceived spontaneously, but one recent prospective study refuted those findings. As well, ARTs contributed 15.5 percent of twins and 43.8 percent of triplets or higher-order multiples in the United States in 2002 (30).

In a study that used Centers for Disease Control and Prevention data regarding infants conceived by the use of ART from 1996 to 2000, the proportion of singletons born preterm and of low birth weight did not change over this period. The percentage of infants born with VLBWs declined overall, although for thawed embryos there was a 42 percent increase in VLBW infants. Singletons conceived by the use of ARTs had an increased risk for all five perinatal outcomes (LBW, VLBW, preterm delivery, preterm delivery and LBW, term LBW), which persisted after adjustment for maternal age, race-ethnicity, and parity (the risk ratios for the outcomes were 1.39 to 1.79). The outcomes for infants conceived by the use of ARTs were compared with secular trends, as there was no control group in that study. The authors concluded that by 2000, the absolute risk for LBW in singletons conceived by the use of ARTs had decreased and that the risk for preterm birth and LBW remained stable (31).

In a case-control study of twins conceived spontaneously compared with those conceived by in vitro fertilization (IVF), it was shown that twins conceived by IVF have a significantly higher incidence of preterm birth and a lower gestational age than twins conceived spontaneously (32).

In a recent prospective multicenter study with a large cohort and concurrent controls, neither ovulation induction nor IVF was significantly associated with increased odds of fetal growth restriction, low birth weight, preterm labor, or premature rupture of membranes (33).

THRESHOLD OF FETAL VIABILITY

Given the substantial, but improving, confidence interval on prenatal estimates of gestational age and fetal weight, neonatologists generally reserve the final decision about delivery room resuscitation for a fetus at the threshold of viability until the infant has been delivered and can be assessed. The ethical justification of this practice has been the independent moral obligation of the clinician to act in the “best interests” of the infant. When the right decision is unclear, the wishes of the parents become determinative. Recently, two court decisions have supported the strategy of resuscitation decision making
at the time of delivery, yet are open to misinterpretation in the direction of overtreatment. In addition, the significance of parental input and consent has been challenged by the court decisions. Some empirical data from the United States and abroad suggests variation of resuscitation practices at 24 weeks of gestation (23 completed weeks), but at less than 23 completed weeks, clinicians consider resuscitation to be of minimal benefit. Professional guidelines strongly advocate parental involvement in decisions made at the limit of viability.

**Legal Cases Concerning Delivery Room Resuscitation**

**Miller v. HCA (Texas, 2003)**

The 2003 decision of the Texas Supreme Court in the case of Sidney Miller, a 615-gram, 23-week-gestation preterm infant born in 1990 and resuscitated against the wishes of her parents, affirmed the privilege of the physician to overrule parental wishes in emergent circumstances. The court concluded that the decision of whether to resuscitate an extremely premature infant can be made only at birth, at which time a physician can examine the infant (13).

In a commentary on the *Miller* decision, Annas agreed that “an informed decision … can be made only by actually examining the infant at birth.” His concern was that clinicians may use the rules in a way they were not intended to support uniform resuscitation of newborns born preterm. “More troubling, the court implies that life is always preferable to death … and thus could be interpreted in the future to support the neonatologist who always resuscitates newborns, no matter how premature…. [S]uch a neonatologist is not exercising any medical judgment or making a split-second decision…. [T]he decision … has been made at a time during which the court believes it cannot reasonably be made: before the birth” (34).

**Montalvo v. Borkovec (Wisconsin, 2002)**

Emanuel (Montalvo) Vila was born in Wisconsin in 1996 at 23 3/7 weeks and with a birth weight of 615 or 679 grams. He was resuscitated with what his parents report was inadequate information about the prognosis of an infant at his gestational age. In this case, consideration of the requirement of informed consent presumed that the parents had a right to decide not to resuscitate the newly born child or to withhold LSMT. This presumption was incorrect, because the Wisconsin Supreme Court (*In re Edna*, 1997) concluded that withholding or withdrawing LSMT was not in the best interest of any patient who is not in a persistent vegetative state (PVS). In Wisconsin, in the absence of PVS, the right of a parent to withhold LSMT from a child does not exist (35).

The Wisconsin court also applied the federal child abuse amendments (i.e., the “Baby Doe” regulations) to the *Montalvo* case, arguing that because Wisconsin fulfilled the obligations for federal funds, Child Abuse Protection and Treatments Act (CAPTA; 1984) regulations were applicable in the case. CAPTA prevents “withholding of medically indicated treatment” defined as “failure to respond to the [disabled] infant's life-threatening conditions by providing treatment … which, in the treating physician’s … reasonable medical judgment, will be … effective in … correcting all such conditions.” The option of withholding resuscitation, argued by the plaintiffs, was exactly what CAPTA prohibited, regardless of gestational age or birth weight. Emanuel’s parents did not have the right to withhold or withdraw immediate postnatal care because he was neither dying nor comatose. Because there was no alternative to treatment, the informed consent process was unnecessary. In Wisconsin, the informed consent statute states that it is unnecessary to disclose “information in emergencies where failure to [treat] would be more harmful to the patient than treatment.” “In the exigent circumstances confronting the treating physician here … failure to treat was tantamount to a death sentence. Under the pleaded circumstances, informed consent was not required” (35).

**Recent Legislation Defining Personhood**
In 2002, the 107th U.S. Congress passed the Born-Alive Infants Protection Act of 2001. This law established personhood for all infants who are born “at any stage of development” who breathe, have a heartbeat, or “definite movement of voluntary muscles,” regardless of whether the birth was due to labor or induced abortion (36). In the House Judiciary Committee’s accompanying report, it was stated that the infant is “a person under the law—regardless of whether the child’s development is believed to be, or is in fact, sufficient to permit long-term survival.” The report goes on to acknowledge the uncertainty of whether infants below certain birth weights should be treated and states that “the standard of medical care applicable in a given situation involving a premature infant is not determined by asking whether that infant is a person…. HR 2175 would not affect the applicable standard of care” (37). In a brief commentary on the law, the Neonatal Resuscitation Program Steering Committee of AAP maintained that the act should not affect the current approach to treating the extremely premature infant and that comfort care was still an option for infants for whom resuscitation or continuation of life support is deemed inappropriate (38).

Empirical Data Concerning Limits of Viability in Current Practice in the United States and Abroad

The emerging professional standard of care in the United States and most Western nations appears to be full resuscitation for premature infants born at greater than 24 weeks gestational age and no resuscitation for premature infants born at less than 23 weeks gestational age. Parental wishes appear to have a role for infants born at between 23 and 24 weeks gestation but have a limited impact outside of that range.

In a survey of practicing neonatologists in Massachusetts conducted in 2002, differences in the perceived limits of viability were seen (41 percent of physicians saw treatment at >24 weeks gestation as clearly beneficial, and 84 percent saw treatment at >25 weeks gestation as clearly beneficial). At 23 weeks gestation or less, 93 percent of physicians considered resuscitation to be of no benefit. At 24 1/7 to 24 6/7 weeks gestation, physicians were split: 40 percent of physicians considered treatment to be beneficial and 60 percent considered the benefits to be uncertain. Thirty-three percent of physicians would resuscitate an infant upon parental request even if they considered the treatment to be of no benefit. When treatment benefits are uncertain, 100 percent of physicians would resuscitate the infant at parental request, 98 percent would resuscitate the infant if the parents were unsure, and 76 percent would withhold treatment at parental request. In addition to parental preferences, when the benefit of treatment was uncertain, factors that physicians thought were very important to consider were the medical condition of the infant at delivery (68 percent) and the likelihood of death (63 percent). Ninety-one percent of the respondents considered potential long-term suffering of the infant to be important or very important. The authors concluded that most respondents would provide treatment that was beneficial, withhold treatment that was of no benefit, and defer to the parents’ requests when the benefits were uncertain (39).

In a survey of neonatologists and neonatal nurses at Australian perinatal centers in 1997 and 1998, the majority of neonatologists (85 percent) and nurses (88 percent) would “always” or “almost always” resuscitate infants at 24 weeks gestation. More than half of respondents would occasionally resuscitate infants with birth weights of between 400 and 500 g. The most important factors influencing resuscitation decisions were parental wishes and the presence of congenital anomalies (40).

As part of the EURONIC project (a European questionnaire study examining the attitudes and practices of neonatal physicians and nurses), a case of extreme prematurity was presented and attitudes were assessed. At 24 weeks gestation, with a birth weight of 560 g, and with a 1-minute Apgar score of 1, 82 to 98 percent of physicians would resuscitate an infant in all countries studied except the Netherlands, where only 39 percent of the physicians surveyed would resuscitate the infant. The authors concluded that most physicians (except those in the Netherlands) considered this extremely preterm infant viable. Decision-making attitudes and practices after the infant’s deterioration varied by country (41).

In an expert panel of North American neonatologists, pediatricians, and intensive care physicians, questions were asked regarding the initiation or withdrawal of treatment for several cases of ELBW
infants. The principles that emerged from discussions of these cases were as follows: (a) that it is “difficult to make definite plans for treatment or non-treatment until the baby is born, and the neonatologist has a chance to assess size, maturity, and clinical status”; (b) that it is “essential to avoid misleadingly absolute predictions of viability or non-viability”; (c) that “shared and dynamic decision-making … ensures that decisions incorporate parental values, the infant’s interests, and an optimal understanding of the facts and the inherent uncertainties in the child’s clinical situation”; and (4) finally, that “in order for parents to choose to forgo life sustaining treatment on their child’s behalf, survival does not have to be impossible or unprecedented—it only has to be very unlikely” (8).

In a questionnaire completed by 17 of 18 neonatologists in Alberta, gestational age was the most important factor involved in the decision to resuscitate or not resuscitate an infant. Parental requests, birth weight, and multiple anomalies also were important factors. Factors that were not important to the neonatologists included costs, medical-legal factors, and the religious beliefs of the physicians (42).

A longitudinal cohort study of live births at between 23 and 26 weeks gestation at the University of North Carolina in 1994 and 1995 found that 29 percent of infants were resuscitated at 23 weeks gestation, 67 percent were resuscitated at 24 weeks, 93 percent were resuscitated at 25 weeks, and 100 percent were resuscitated at 26 weeks. The likelihood of resuscitation was associated with increasing gestational age, higher birth weight, a better prognosis for survival and quality of life, and greater physician uncertainty about the accuracy of the prognosis. Withholding of resuscitation at delivery was associated with parental (not physician) preference for comfort care only. When physicians would have preferred comfort care only, resuscitation was provided in half of the live births. Physicians’ prognoses for survival were relatively accurate. The authors concluded that physicians were more likely to resuscitate extremely preterm infants when the prognosis was uncertain or the parental wishes were unknown. When the parental wishes were known, parents usually determined the amount of resuscitation performed at delivery (43).

Professional Guidelines for Decision Making at the Limits of Viability

Professional guidelines advocate a model of joint decision making between parents and clinicians at the limits of viability, within the limits of appropriate medical care. However, the margins of viability at which parental discretion becomes a factor are increasingly limited (i.e., at between 23 and 24 weeks gestational age).

AAP provides guidelines for counseling and assisting families who face the delivery of an extremely preterm infant. The recommendations include (a) frequent reevaluation of the fetus or infant to assist in decision making and prognosis; (b) joint decision making with the family; (c) appropriately informing parents regarding “maternal risks associated with delivery options, potential for infant survival, and risks of adverse long-term outcomes”; (d) respect for parental choices in management within the limits of appropriate medical care; and (e) physician education about local and national outcomes associated with extremely preterm birth (44).

Despite all that is known about survival and outcomes at “periviable” gestational ages, the conclusions of a recent AAP workshop on the topic were primarily that major gaps in knowledge still exist and require study. Both obstetric and neonatal knowledge gaps exist, including the need for (a) improved gestational age and maturity assessments; (b) knowledge of the optimal mode of delivery; (c) studies on optimal delivery room management; as well as (d) evidence for appropriate management of nutrition, medications, infections, and other interventions in the postnatal period (45).

WITHHOLDING AND WITHDRAWING LIFE-SUSTAINING MEDICAL TREATMENT

The withholding and withdrawal of LSMT for infants are practiced in the United States and abroad. A significant number of preterm infants die with some limitation to their treatment. Most often, these are
infants who are moribund and likely to die whether or not treatment is continued, but LSMT may also be withdrawn when long-term quality-of-life issues are the primary concern. Several authors speculate that the high rate of withholding or withdrawing life support is related to the sizeable number of extremely premature infants who are given initial trials of therapy. Over the last decade, the length of the initial trial appears to have increased dramatically. Ethicists and pediatricians have speculated that the Baby Doe regulations of the 1980s have affected clinicians’ willingness to withhold or withdraw life support for newborns. Despite the Baby Doe regulations, AAP statements and guidelines continue to endorse the practice of limiting life support for critically ill infants with poor prognoses. Published data on end-of-life practices in parts of northern Europe have demonstrated that a minority of European physicians is willing to actively hasten death in critically ill neonates. Finally, familiarity with the use of pain management and palliative care is increasing.

Empirical Data Concerning Withholding and Withdrawing LSMT

Physicians have reported their experiences of withholding or withdrawing LSMT for infants in the medical literature since the 1970s. Several single-center studies have documented their practices of withholding or withdrawing LSMT. Prospective research is needed to accurately describe how these decisions are being made in modern clinical practice.

In 1973, Duff and Campbell at Yale published an early U.S. account of the limitation of medical treatment in the newborn period (primarily for term infants with congenital anomalies). In their retrospective review, 14 percent of deaths in the Yale nursery during a 2 1/2-year period were associated with the discontinuation of life-sustaining treatments. The authors concluded that families should be the primary decision makers, with guidance from society and health care professionals. The authors’ discussion raised many questions about the ethics of withholding or withdrawing treatments, including issues around unclear prognosis, informed consent, and proxy decision making (46).

A similar case series from the 1980s at Hammersmith Hospital in London examined all cases in which withdrawal of treatment was discussed by the medical team over a 4-year period. Most of the infants in this series were born preterm or had acquired neurological damage. Of the 75 infants for whom withdrawal of treatment was discussed, 51 of their families were offered withdrawal by the medical team. In 47 cases, the families accepted the decision, and in 4 cases the families chose continued intensive treatment. The author concluded that withdrawal of treatment was the best course of action for infants who were certain to die or have “no meaningful life.” He also concluded that effective communication and trust between physicians and families should preclude the need for involvement of the law or ethics committees (47).

A retrospective review of deaths in the NICU at the University of California at San Francisco (UCSF) between 1989 and 1992 documented the circumstances of the 165 infants who died during that period. One hundred eight died after the withdrawal of life-sustaining treatments, and another 13 died after additional treatments were withheld. A total of 73 percent of the deaths were attributable to the limitation of life-sustaining treatments. In the records of three-quarters of the infants whose treatments were withheld or withdrawn, the neonatologist documented the belief that continued treatment was futile and that death was imminent. In half of the infants’ records, quality-of-life concerns were documented as a reason to limit treatment. For nearly one-quarter of the deaths, physicians cited quality-of-life concerns as the sole reason for the limitation of treatment. These findings were noted in the context of active delivery room resuscitation of 91 percent of live-born infants with birth weights of between 500 and 799 grams. In the cohort studied, the sequelae of extreme prematurity caused the highest proportion of deaths attributable to the withholding or withdrawal of therapies. The authors concluded that “the widespread application of neonatal intensive care has likely increased the proportion of infants for whom aggressive treatment is attempted but for whom it is subsequently determined to be ineffective or inappropriate.” Conclusions from this study are limited by its retrospective design and an inability to abstract details of the decision making from the medical records (48).
In a case series of NICU deaths from Pittsburgh, Pennsylvania, 82 percent of deaths occurred after some limitation of treatment. In three-quarters of the deaths, the parents were involved in the decision to limit treatment, and disagreement between the parents and the care providers was rare. The authors concluded that decision making near the end of life for a critically ill neonate frequently results in limiting LSMT. They conclude, like the UCSF group, that “the rise in proportion of deaths after a decision of this nature may relate ... to the increased number of extremely low birth weight infants who are given trials of aggressive therapy” (49).

A retrospective review of NICU deaths in 1988, 1993, and 1998 at the University of Chicago revealed local trends in withholding cardiopulmonary resuscitation (CPR) and withdrawal of LSMT. In 1993 and 1998, nearly 70 percent of nonsurvivors died without receiving CPR, which was a significant increase from the 16 percent in 1988. In 1993 and 1998, ~40 percent of all nonsurvivors died after withdrawal of mechanical ventilation, and ~40 percent of those infants for whom mechanical ventilation was withdrawn were hemodynamically stable. The vast majority of infants whose ventilation was withdrawn were full-term infants with congenital anomalies or asphyxia. Only rarely was ventilation withdrawn from ELBW in- fants with severe neurological injuries (<5 percent in all 3 years studied). Interestingly, the median and the average day of death did not differ significantly between the 78 nonsurvivors whose interventions were limited and the 100 nonsurvivors who received full intervention. The authors conclude that in their NICU, there has been a welcome increase in the number of infants who die in the arms of their parents, after removal of endotracheal tubes and without receiving CPR. They also suggest that a more nuanced examination of withholding and withdrawing therapies in the context of both physiologically stable and moribund infants is necessary to better understand the circumstances of end-of-life decision making (50).

Whether aggressive treatment of an ELBW infant is futile in terms of long-term survival is difficult to determine, as accurate predictors of survival have remained elusive. Researchers at the University of Chicago have raised the concern that a by-product of improved care and survival of ELBW infants is that the length of stay (LOS) for nonsurvivors has significantly increased. In a retrospective examination of ELBW (birth weight of <1,000 grams) infant survival at the University of Chicago during the 1990s, the median LOS for nonsurvivors rose steadily from 2 days in 1991 to 10 days in 2001. The authors concluded that the NICU “trial of therapy” for ELBW infants now takes much longer than it has in the past, and asking parents to “hold their breath” for 2 or 3 days to await improved prognostic estimates is no longer feasible (51).

**Impact of the Baby Doe Regulations of the 1980s**

The so-called Baby Doe regulations are often interpreted in a way that challenges physicians’ authority to withdraw or withhold LSMTs from ELBW infants. In fact, in the Montalvo decision (2002) the Wisconsin court explicitly cited the regulations in arguing against a parental right to withhold resuscitation. However, these rules were not originally intended to apply to premature infants; rather, they were intended to apply to disabled full-term infants (35).

The original Baby Doe regulations (1984) were based on Section 504 of the Rehabilitation Act of 1973 and were struck down by the U.S. Supreme Court in 1986. The regulations held that nontreatment was discriminatory and violated an infant’s civil rights.

The second set of Baby Doe regulations was enacted in 1984 and went into effect in 1985. They are amendments to CAPTA, which require the continuation of medical treatment unless an infant is “chronically and irreversibly comatose”; “the provision of such treatment would merely prolong dying, not be effective in ameliorating or correcting all of the infant’s life-threatening conditions”; or “the provision of such treatment would be virtually futile in terms of the survival of the infant and the treatment itself under such circumstances would be inhumane.” Adherence to these rules is required for states to receive federal child abuse funds. The existing rules have remained untested in the Supreme Court (52).
Interpretation of the Baby Doe regulations has been laden with pitfalls. The diagnosis of coma in the newborn period is impossible, and the concept of futility is too vague and subjective to be useful in decision making.

The Baby Doe regulations have affected the care of infants, including ELBW infants, as reflected in the attitudes of neonatologists. A questionnaire sent to members of the AAP Perinatal Section 1 year after the Baby Doe regulations went into effect asked physicians to consider several difficult neonatal cases and assessed their attitudes regarding the impact of the Baby Doe regulations. The results revealed that 30 percent of neonatologists thought that the Baby Doe regulations required the continuation of mechanical ventilation in a 550-gram preterm infant with seizures and a large intracerebral hemorrhage. Twenty-three percent of physicians stated that their approach to this case had changed as a result of the Baby Doe regulations. Eighty-one percent of those who responded did not think that the regulations would result in improved care for infants. Three-quarters did not believe that the regulations were needed to protect handicapped infants’ rights. Kopelman et al., the study's authors, concluded that the regulations were not necessary and that they minimized the role of parents in decision making. The conclusions are limited by the survey methods of the study and the 49 percent response rate. The author also discussed additional concerns about the regulations, including concerns about the poor use of resources, difficulties with determining unconsciousness in the newborn period, changes in medical standards of care, and undermining of the best-interests standard in caring for ill neonates (53).

Kopelman, in commentaries 20 years after the enactment of the Baby Doe regulations, argued that AAP has interpreted the Baby Doe regulations incorrectly. She remains concerned that the regulations do not allow individualized decision making and use of the best-interests standard that AAP promotes. She disputes the benign interpretations of the terms of the regulations as understood by the AAP leadership and the Committee on Bioethics. She also argues that the rules are mistaken, as they do not allow for clinician discretion and do not treat infants in a way that adults would wish to be treated with regard to the relief of suffering. She raises concern that the Baby Doe rules have recently been applied in the Montalvo case in Wisconsin, where the appeals court decided that the parents had no right to decline treatment, as their 23-week-gestation infant was neither comatose nor dying (11, 54–56).

Professional Guidelines for Limitation of LSMT in the United States

There have been efforts over the past 15 years to develop a professional consensus on the limitation or withdrawal of LSMT from ELBW infants. Various committees within AAP have published guidelines for limiting life-sustaining treatments for newborns.

A group of prominent North American neonatologists, pediatricians, and intensive care physicians convened to review questions regarding the withdrawal of treatment for ELBW infants. The results of their discussions were published in 1994. The consensus of the group included the statement that “in order for parents to choose to forgo life sustaining treatment on their child’s behalf, survival does not have to be impossible or unprecedented—it only has to be very unlikely.” They acknowledge the uncertainties of prognosis, while emphasizing the importance of shared decision making between families and medical professionals. The group also discussed end-of-life decisions for chronically ill infants and concluded that a shared approach to decision making, with consideration of the child’s suffering, the effects on the family, and the long-term prognosis, is the best course of action (8).

In 1994, the AAP Committee on Bioethics published Guidelines on Forgoing Life-Sustaining Medical Treatment. The general principles recommended were as follows: a presumption in favor of treatment, the patient or surrogate’s right to decide and be informed, the patient or surrogate’s right to refuse treatment, the fact that decisions to forgo treatment are limited to the specific treatment in question (not necessarily to all treatments), the preservation of respect for the patient, physicians’ obligations to arrange for the care of their patient if they do not wish to participate in limiting LSMT, and the presumption against judicial involvement unless there are irresolvable disputes. The committee advocates the best-interests standard
as a guideline for decision making for neonates. The document also emphasizes the importance of physician documentation in cases of limitation of LSMT (57).

A year later, the AAP Committee on Fetus and Newborn published “The Initiation or Withdrawal of Treatment for High-Risk Newborns.” That document recommended the approach of the individualized prognostic strategy: providing care at an appropriate level at the time of initiation of care with constant reevaluation of the infant and dynamic decision making. Parents are to be informed and involved in decision making that could affect the infant’s outcome. One physician should act as the spokesperson for the medical team. Treatments should be discontinued when “the condition is incompatible with life or when the treatment is judged to be futile” (9).

In 1996, the AAP Committee on Bioethics published Ethics and the Care of Critically Ill Infants and Children. The committee expressed concerns that the Baby Doe regulations had caused physicians to overuse LSMT. However, the committee suggested that the language used in the regulations “may permit more physician discretion than some realize.” The committee recommended parental involvement in decision making with physicians, using the principles of informed parental permission, and opposed clinical decision making on the basis of resource limitation (58).

**End-of-Life Practices Abroad**

European end-of-life practices vary by country, but there is great concern about the practice of active euthanasia in the Netherlands, France, and Belgium. A recent publication suggested a protocol designed to allow and regulate euthanasia of newborns in the Netherlands (59). In addition, infants at the border of viability (those born at less than 26 weeks gestation) are resuscitated much less frequently in the Netherlands than in other European countries and the United States. However, physicians in several European countries are uncomfortable with the practice of withholding or withdrawing life-sustaining treatments, according to the current literature.

**EURONIC Data**

The EURONIC research project has been carried out primarily in eight European countries and has amassed data via anonymous questionnaires on end-of-life practices and attitudes in neonatal intensive care self-administered to physicians and nurses.

In all countries, between 61 and 96 percent of the neonatologists reported that they had ever decided to limit intensive treatment. Between countries, a wide range of proportions of physicians withdrew ventilation, from a low of 23 percent in Italy to a high of 93 percent in the Netherlands. In that study, 86 percent of physicians in France and 45 percent of physicians in the Netherlands reported that they had given medications with the purpose of ending life. They conclude that variations in practice are culture and country dependent (60).

In a report that measured physicians’ attitudes regarding quality of life versus absolute value of life, the country of origin remained the strongest predictor of physician response. Attitude scores were higher (i.e., indicating a greater concern for quality of life) in the Netherlands, the United Kingdom, and Sweden and lower (indicating a greater concern for life in general) in Hungary, Estonia, Lithuania, and Italy. The group concluded that increased concern for quality of life was associated with physicians’ likelihood of reporting that they had ever set limits to intensive interventions. After controlling for potential confounders such as age, gender, years of experience, and religion, there were still important differences between countries, “suggesting an effect of cultural and social factors” (61).

**Other European Empirical Data on End-of-Life Care**
A questionnaire given to physicians caring for neonates in the Netherlands showed that during a 3-month period in 1995, 37 percent of neonatal deaths occurred following the administration of potentially life-shortening drugs. In 22 percent of cases, hastening of death was partially intended, and in 26 percent of cases, hastening of death was explicitly intended. In the vast majority of these cases (88 percent), the decision had been discussed with the infant's parents. The authors concluded that it is difficult to make the distinction between giving adequate palliative therapy for pain and discomfort and intentionally hastening death (62).

In a Belgian study, anonymous questionnaires regarding end-of-life decisions were sent to the attending physicians of infants who died over a 1-year period (in 1999 and 2000). Of the 194 nonsudden deaths during that year, 44 percent were preceded by a decision to withhold or withdraw treatment, 21 percent of infants were given opioids at doses that could be potentially life shortening, and 9 percent of patients received lethal doses or lethal drugs. Of the 143 deaths preceded by end-of-life decision making, half of the deaths occurred with the physician's explicit intention to hasten death. Lethal drugs were used five times more often for early neonatal deaths than for later deaths; and they were mainly used for preterm infants with intracerebral hemorrhage, infants with severe congenital malformations, and preterm infants with congenital malformations. In the attitude study, 79 percent of physicians thought that it was sometimes the physician's duty to prevent suffering by hastening death. The authors concluded that in the early neonatal period the severity of disorders is more apparent and that decisions based on estimates of survival are more easily made. They also concluded that the widespread willingness of physicians to participate in life termination is related to physicians’ acceptance of best-interest standards and recognition of quality-of-life considerations (63).

In another study comparing end-of-life decisions in the Netherlands in 1995 and 2001, it was concluded that practices had changed little. Physicians completed questionnaires after the deaths of their patients. End-of-life decisions were made for 62 and 68 percent of all deaths in 1995 and 2001, respectively. Possible life-shortening drugs were used in 23 and 29 percent of patients who died after withholding or withdrawal of life-sustaining treatments. In 8 percent of deaths (in both years) following the withholding or withdrawal of life-sustaining treatments, drugs were given with the intention of hastening death. In 2001, more than 70 percent of end-of-life decisions were made because the infants had no chance of survival, and 23 percent were made because of a poor prognosis for later life. The authors concluded that despite liberal regulations around active ending of life in the Netherlands, the frequency of the practice had not increased (64).

**Pain Management and Palliative Care at the End of Life**

Despite concerns about respiratory depression and active ending of life, the use of opioids for pain management and analgesia is widespread after the withdrawal of life-sustaining therapies. There is also evidence, albeit sparse, that familiarity with and the use of palliative care in neonatology is increasing.

In a retrospective review of NICU deaths in a single center in the United States (from 1989 to 1992), 84 percent of infants received opioid analgesia when life support was withdrawn or withheld. The majority (64 percent) received doses in the usual pharmacologic range, whereas 36 percent received higher doses. (Ninety-four percent of those receiving suprapharmacologic doses had been receiving opioid analgesia previously and were likely to have developed tolerance.) The median time of death was 18 minutes for infants receiving pharmacologic doses of morphine and 20 minutes for infants receiving higher doses. All infants who died of necrotizing enterocolitis received opioids. The authors suggested that morphine was considered necessary treatment for abdominal pain in infants dying of necrotizing enterocolitis. Because of the methods used in the study, it was difficult to conclude anything about the physicians’ intentions in administering analgesia (65).

A prospective study in the pediatric ICU literature showed that 89 percent of patients who were withdrawn from ventilatory support received sedation and analgesia. In patients who received analgesia or sedation as the ventilator was being withdrawn, the reasons for administering these medications that the physician
and nurse stated were important were to decrease pain (83 percent), decrease anxiety (77 percent), and decrease air hunger (74 percent). Only 2 percent of physicians believed that it was important to give sedation and analgesia to hasten death (66).

At Children’s Hospital of Wisconsin, a retrospective chart review evaluated the use of palliative care services in patients less than 1 year of age who died in the hospital over a 4-year period. Thirteen percent of infants who died had received a palliative care consultation, and the percentage had increased from 5 percent in 1994 to 38 percent in 1997 (the study was limited by the small number of patients). Those infants who had a palliative care consultation had fewer interventions, including blood product administration, blood draws, central lines, feeding tubes (including surgically placed tubes), endotracheal tubes, radiographs, and paralytic agent administration. There was also an increased rate of provision of supportive services, such as social work and pastoral services, for the palliative care patients. The authors concluded that palliative care services are still underutilized, but for patients who have consultations, the numbers of invasive and uncomfortable interventions are decreased. The study is limited by its small sample size and the exclusion of a significant number of patients who died at home after palliative care consultation (67).

The Concept of Futility in the Care of Extremely Ill Infants

Although much has been written about the concept of futility, there is a lack of agreement on its definition and of its utility as a concept. Within the realm of neonatal care, the concept has been invoked in cases both of extreme prematurity and of severe congenital anomalies that are incompatible with survival.

Futility arguments have been invoked when the health care team disagrees with parents regarding the provision of life-sustaining treatments to critically ill or severely neurologically impaired infants. Futility has been conceptualized in several ways, including physiological, or quantitative, futility; qualitative futility; resource-centered futility; professional integrity-based futility; and patient-centered, or goal-driven, futility (68). All but (probably) the concept of physiological futility are determined by the beliefs and values of the individuals involved in decision making. In a review article on decision making in extreme prematurity, Campbell and Fleischman assert that “although the concept of physiological futility provides a nearly value-free understanding of futility, it is not helpful in providing guidance about treatment decisions for infants for whom the level of benefit of the treatment and the overall prognosis is uncertain (69).

Bioethicists Veatch and Spicer contend that care is labeled futile “either because the care produces no demonstrable effect at a chosen level of probability, or because, even though it produces an effect, that effect is believed by the speaker to be of no net benefit” (70). Some authors have suggested that the concept of futility should be considered only in relation to specific treatment goals (68).

The paradigm case for futility conflicts for infants was the case of Baby K, an anencephalic infant born in Virginia in 1992. Although she was not a preterm infant, court rulings in her case could potentially be applied to decisions regarding the resuscitation of infants at the margins of viability or the continuation of life-sustaining treatment for neurologically devastated infants.

Although mechanical ventilation was not the standard of care for anencephalic infants, Baby K’s mother insisted that she be ventilated after birth. Over the ensuing 2 years, the infant intermittently received mechanical ventilation for subsequent episodes of respiratory distress. The treating hospital went to court to have a guardian appointed and to obtain a declaratory motion to allow the provision of palliative care for the infant. The district court ruled that the hospital was required to continue to provide emergency treatment for respiratory distress under the Emergency Medical Treatment and Labor Act (EMTALA). In an appeal, the hospital argued that ventilating an anencephalic infant was not within normal standards of care, but the appeals court ruled that the hospital was required to provide care because the emergency condition was not anencephaly but respiratory distress. The court did, however, acknowledge that the EMTALA laws were not designed for application to this type of case. Court records document that the infant’s mother objected to the limitation of treatment on religious grounds (71, 72). At least one author
argues that parental religious beliefs should be respected in treatment decisions. Post is concerned that religious freedom and the free exercise clause of the First Amendment are at stake when religious concerns are ignored or trivialized during decision making (72).

Veatch and Spicer consider the physician's role limited in determining what treatments are futile. They define the problematic cases as ones in which the treatment has an effect, but it is an effect that clinicians believe has no benefit. They argue that in such cases, it is incorrect to refer to futility on medical grounds. The authors also maintain that in cases in which futility is considered, if the patient is competent or has clearly expressed wishes to have the treatment in question, he or she should receive the treatment, on the basis that the beliefs and the values of the patient or surrogate should take precedence. If the patient is incompetent and the treatment produces harm or pain for the patient, the clinician should seek to override the surrogate decision maker. If the patient is incompetent and the treatment is not injurious, there is no moral reason to override the surrogate. The only exceptions are in the case of compromising the clinician's professional integrity or unjustly using society's resources. The authors believe that the values of the patient or surrogate should take precedence, because clinicians' expertise is limited to medical knowledge and skills, not value judgments (70).

Whether aggressive treatment of an ELBW infant is futile has remained difficult to determine, as accurate predictors of survival have remained elusive. Some researchers have raised the concern that a by-product of improved care and survival of ELBW infants is that the LOS for nonsurvivors has significantly increased. In a retrospective examination of ELBW (birth weight of <1,000 grams) infant survival at the University of Chicago during the 1990s, the median LOS for nonsurvivors rose steadily from 2 days in 1991 to 10 days in 2001. The authors conclude that the NICU "trial of therapy" for ELBW infants now takes much longer than it has in the past, and asking parents to "hold their breath" for 2 to 3 days to await better prognostic news is no longer feasible (51).

SOCIETAL IMPLICATIONS OF PRETERM BIRTH

In the United States, where health care costs account for 15 percent of the gross domestic product, the costs of caring for premature infants have been the subject of some inquiry. The American public implicitly appears to be willing to accept the costs of preterm birth, in return for the improved survival of high-risk infants. It remains difficult to assess comprehensively the true costs of prematurity because of the fragmentation of the American health care system. There is a dearth of empirical literature examining the ethical concerns regarding the costs associated with preterm birth.

Several studies from the United States and abroad have examined predictors of the increased financial costs of caring for cohorts of premature infants during the neonatal period and beyond. Recent publications from Australia have evaluated the effectiveness and the efficiency of NICU care over the past 2 decades. In light of questions about the futility of expensive life-sustaining therapies, the costs of caring for nonsurvivors also have been examined and have been found to be small in proportion to the overall costs of caring for premature infants. One author explored whether ethically sound birth weight cutoffs would result in substantial savings to the health care system.

The long-term costs to society of supporting disabled individuals who were born premature have long been a subject of controversy. As a whole, American society has been willing to provide basic social services to support individuals who were born premature infants and seems unlikely to consider limiting health care spending on the basis of the prognosis for the infants' future quality of life. This is in contrast to the model of several northern European countries, in which infants born at less than 26 weeks of gestational age are typically not resuscitated, primarily because of quality-of-life concerns.

Access to perinatal care has improved in recent years, as more and more women with high-risk pregnancies are receiving care in perinatal centers. Some empirical data have confirmed that premature and LBW infants fare better at higher-level perinatal centers. There are differences in perinatal outcomes
by race, ethnicity, and maternal age; but studies relating ethical concerns to those differences are few and far between.

**Empirical Data on the Financial Costs of Prematurity**

Multiple studies have shown an inverse relationship between gestational age or birth weight and hospital charges during the neonatal period. Preterm or LBW infants are more likely to consume community health services and special education services than term or normal birth weight infants. Families incur substantial long-term costs. It is difficult to measure the true costs (including direct and indirect costs) to patients, their families, and society. Cost-benefit studies are difficult to evaluate (73). In addition, one study empirically examined whether an ethically sound birth weight-specific cutoff for resuscitation would result in substantial savings in the cost of NICU treatment (74).

By using data from large national surveys of health behaviors and medical expenditures, it was estimated that LBW infants incurred more than one-third of all infant health care costs in the first year of life in 1988 ($4 billion of the $11.4 billion spent for all infants). The costs for an individual infant increased as gestational age decreased (75). Similarly, in a single-center retrospective study of preterm infants and hospital charges, gestational age, LOS, and survival were all independently related to cost (76).

In a single-center retrospective review and questionnaire study from an academic medical center in Finland, it was found that ELBW infants incurred significantly increased costs in the first year of life, including hospitalization costs, rehabilitation costs, loss of earnings for care givers, and travel costs. The study was limited by parental recall and participation bias, but the authors concluded that the total costs for ELBW infants, even those who were normally developed, were higher than those for normal-birth-weight infants (77).

The costs of caring for nonsurvivors are less than 10 percent of the overall costs of inpatient care for premature infants. Relative to the total cost of prematurity, the costs associated with NICU “trials of therapy” are small.

In a retrospective look at all ELBW infants born at the University of Chicago between 1991 and 2001, it was found that although the median LOS for nonsurvivors had increased significantly, the NICU bed-days occupied by nonsurvivors remained low (~7 percent) because of the overall improvement in survival (51).

In the retrospective study from Finland, the costs attributed to nonsurvivors constituted 9 percent of overall costs for ELBW infants. The authors concluded that the reason for the low proportion of costs attributable to nonsurvivors was their short life span (77).

A population-based cohort study of ELBW infants born in Victoria, Australia, determined that although the effectiveness of neonatal care had increased from 1979 to 1997 (as demonstrated by threefold increases in survival rates and quality-adjusted survival rates), efficiency (as measured by cost-effectiveness and cost-utility ratios) had remained relatively unchanged in nearly two decades (78, 79).

**Cost and Resuscitation of ELBW Infants**

Stolz and McCormick evaluated whether restricting access to neonatal care on the basis of reasonable birth weight cutoffs would result in substantial cost savings for NICU care. They found that infants born weighing <600 grams accounted for 3.2 percent of NICU charges and infants born at less than 25 weeks of gestation accounted for 5.4 percent of NICU charges. When the number of survivors was assessed at each birth weight cutoff, it was noted, for example, that a cutoff of 700 grams for resuscitation would save 10 percent in NICU costs but that in the United States ~2,700 potential survivors per year would not have been resuscitated. At a 600-gram cutoff, 3.2 percent of NICU charges would be saved, but 575 survivors would not have been resuscitated. In this study, nonsurvivors accounted for 8 percent of resource use by...
VLBW infants. The study was limited by its short-term assessment of costs, the biases incurred by studying the high-risk population of an academic metropolitan medical center, and a time period that spanned the introduction of surfactant. The authors conclude that ethically sound (i.e., extremely low) birth weight cutoffs for resuscitation would not result in substantial savings in the cost of NICU treatment (74).

Tyson et al., using Neonatal Research Network data, examined survival rates and LOSs for infants born weighing between 501 and 800 grams. That group estimated LOS at 127 hospital days per survivor and 148 days per survivor without severe brain injury. If mechanical ventilation had been used for all infants, the authors estimated a significant increase in resource use for eight additional survivors per 100 infants in this birth weight category (80).

A population-based study compared infants born at 23 to 26 weeks of gestation in the 1980s in New Jersey and the Netherlands, where treatment and resuscitation strategies were (and still are) quite divergent. The investigators found that the aggressive treatment strategies in New Jersey were associated with 24 additional survivors per 100 live births and 1,372 additional ventilator days per 100 live births. The prevalence of disabling cerebral palsy was also significantly increased among the survivors in the New Jersey cohort. The authors acknowledge the moral dilemmas inherent in strategies of either universally or selectively initiating intensive care (81).

Educational and Social Costs of Prematurity

The increases in long-term costs for individuals who were born premature are due to medical costs as well as educational and social costs. These individuals often require rehospitalization, specialized medical care, and special education or early intervention services. There are additional costs to their families, including transportation costs and the loss of wages if one parent leaves the workforce to care for the child.

In a population-based study conducted in the United Kingdom, it was shown that the total duration of hospital admissions during the first 5 years of life for individuals born at <31 gestational weeks was almost eight times that for individuals born at term. The largest component of the cost was the initial birth admission, but the cost differences persisted through the subsequent 4 years of life. Gestational age at birth was the strongest predictor of total costs during the first 5 years of life. The authors concluded that prematurity was a major predictor of the cost of medical services during the first 5 years of life (82).

Petrou et al. performed a meta-analysis of studies of the long-term costs of preterm birth and LBW. In their analysis, the authors used evidence from 20 studies to conclude that (a) "preterm or low birth weight infants are significantly more likely to be rehospitalized” than term or normal-birth-weight infants; (b) “the increased use and cost of health care services consumed by preterm or low birth weight infants persists into childhood,” with major neurologic abnormalities increasing the families’ use of hospital and outpatient services in the longer term; (c) survivors have high rates of school failure and learning problems, requiring special education services; and (d) families have increased out-of-pocket expenses related to the consequences of prematurity and often have substantial reductions in family income (83).

In population-based surveys assessing medical expenditures and family health, it was noted that children born with LBWs were 50 percent more likely than normal-birth-weight children to require special education services and were slightly more likely to repeat a grade of school (75).

Access to Perinatal Care

In the 1980s and 1990s, perinatal care was regionalized in an attempt to improve maternal and neonatal outcomes. Women with complicated pregnancies were referred to higher-level perinatal centers for specialized care and neonatal therapies. It now appears that deregionalization is occurring, as the need
for neonatal intensive care continues to grow (84). Community hospitals have begun offering intensive therapies, such as high-frequency ventilation and nitric oxide, raising concerns about quality of care. The ethical concerns that have arisen as a result of this deregionalization include the following: (a) parents who are less savvy or less informed may not be aware that their premature infant is not being treated at a perinatal center of the correct level, and (b) clinicians may be inadequately trained to use intensive therapies. As shown by the data that follow, premature infants delivered at hospitals without the proper level of neonatal care may have worse prognoses. One retrospective study looking at the outcomes for infants with necrotizing enterocolitis and mortality showed no difference in outcomes whether or not there was immediate access to surgical care. The study’s conclusions are limited by its methodology.

Empirical Data Concerning Access to Perinatal Care

In a population-based cohort study done in South Carolina (from 1993 to 1995), total birth weight-adjusted mortality rates were significantly higher in Level I and II perinatal centers than in Level III centers (as many as 267 deaths per 1,000 births in Level I centers down to 146 deaths per 1,000 births in Level III centers [p < 0.05]). There was a trend toward lower mortality rates among VLBW infants born in Level III centers, although the numbers for some subgroups were too small for the trend to reach statistical significance (85).

In a population-based cohort study in Georgia (from 1994 to 1996), it was determined that 77 percent of VLBW infants were born at Level III or IV centers, 9.8 percent were born at Level II+ hospitals, and 13.1 percent were born at centers with other levels. The neonatal mortality rate, after adjustment for birth weight, correlated with the level of the perinatal center, with the lowest rate found for infants born at Level III centers (127.8/1,000 births) and the highest rate found for infants born at Level II centers (276.2/1,000 births). (Mortality rates were higher for infants born at Level IV hospitals [181.8/1,000 births] than at Level III centers because of the nature of the patient population.) The authors concluded that the highest mortality rates were at the centers with the lowest levels of care, even after consideration of the differences in the populations delivering at hospitals with various levels of care (86).

In a Swedish population-based cohort study, infants born at between 24 and 27 weeks (from 1992 to 1998) had increased mortality rates at general hospitals (32 percent) compared with those at university hospitals (23 percent). There was no difference in mortality rates for infants born at between 28 and 31 weeks gestation when the rates were compared by hospital type. The authors concluded that extremely preterm infants born at general hospitals suffered a substantially increased mortality rate. They question whether additional centralization may improve survival (87).

In a retrospective Australian review of outcomes for infants with necrotizing enterocolitis, infants cared for in centers with neonatal surgical facilities had neither improved survival nor improved outcomes such as LOS, resection for strictures, days on total parenteral nutrition (TPN), or mortality compared with the survival rates and outcomes for infants who were cared for in centers without neonatal surgical facilities. The study was confounded by factors that included the differential administration of antenatal steroids to the two groups. The authors concluded that the management of infants with necrotizing enterocolitis in centers without surgical capabilities was not associated with increases in morbidity or mortality (88).

One study conducted in the 1980s examined differences in the incidence of LBW or perinatal mortality between populations residing in metropolitan and nonmetropolitan areas in the United States. By using data from the National Linked Birth Death Data Set obtained between 1985 and 1987, it was found that at the national level, residence in a nonmetropolitan area was not associated with a higher risk of LBW or neonatal mortality, although the risks of postneonatal mortality and the late onset of prenatal care were slightly higher. The authors concluded that “non-metropolitan residence is not a strong risk factor for low birth weight outcome and neonatal mortality in the United States.” The study was limited by its inability to assess other morbidities and by the fact that the data were collected in the mid-1980s, after which time major changes in clinical practice and mortality have occurred (89).
Race and Ethnicity and Access to Medical Care

Insidious racism or ethnic prejudice on the part of obstetricians or neonatologists may affect access to proper treatments. In a population-based retrospective cohort of women delivering singletons in the United States between 1989 and 2000, it appeared that preterm birth rates were declining among African American women (18.5 percent in 1989 versus 16.2 percent in 2000), although they were still substantially higher than the preterm birth rates among white women (9.4 percent in 2000). The numbers of medically indicated preterm births rose among both African American and white women, although they rose to a much higher degree among white women (an increase of 32 percent for African American women and an increase of 55 percent for white women). The authors concluded that the increase in preterm birth rates among white women was largely due to an increase in medically indicated preterm birth, whereas in African American women the preterm birth rate declined because of decreased rates of preterm rupture of membranes and spontaneous preterm birth. The authors raised concerns about the racial differences in obstetric interventions (90).

Distributive Justice and the Care of Preterm Infants

Ethical concerns about the distributive justice of caring for premature infants in light of the incidence of prematurity in high-risk populations of low socioeconomic status may be overstated, as the epidemiology of prematurity is changing. Rates of premature birth remain excessive in African American women, adolescents, and women of low socioeconomic status. Thus, there remain differences in perinatal outcomes between women of high and low socioeconomic status, and in particular, there are significantly poorer perinatal outcomes for African American women in the United States. However, preterm birth rates may be increasing among women of high socioeconomic status as they delay childbearing and use ARTs to conceive. As a result, the proportion of premature infants born to mothers of higher socioeconomic status may be rising. Some data have raised the concern that infants conceived by the use of ART are more likely to be born premature or of low birth weight. Achieving access to high-quality prenatal and obstetric care for all women, regardless of socioeconomic status, race, or ethnicity, would help the realization of justice for pregnant women and neonates.

In a population-based study of birth outcomes in North Carolina (1993 to 1997), it was found that Hispanic and white women had similar rates of infant mortality, low birth weight, and prematurity but that African American women had significantly higher rates of all adverse outcomes. In that study, Hispanic women had less education than African American women but had prenatal care patterns similar to those of African American women. Hispanic women also had significantly lower rates of daily tobacco use than white or African American women. The authors could not explain why, despite similar rates of use of prenatal care use, Hispanic women had significantly better birth outcomes than African American women. They did suggest that health behaviors such as smoking may be an important difference with respect to birth outcomes (91).

In an observational study from Arizona, adolescents had a greater incidence of delivering LBW infants, with 2 percent of their deliveries being VLBW, whereas the rate was 1.1 percent among women at least 19 years old (p = 0.002) (92).

In a large population-based study in New Zealand spanning the years from 1980 to 1999, it was found that the overall rates of premature births rose from 4.3 to 5.9 percent; however, the largest increase was among families living in the least-deprived areas (a 71.9 percent increase, from 3.2 to 5.5 percent). The authors concluded that preterm births were still on the rise, potentially because of changes in ultrasound dating techniques, changes in the definition of viability, decreased numbers of stillbirths, and increased rates of assisted conception. They also concluded that the social gradient in preterm birth had disappeared, with possible reasons including changes in maternal age and parity and women’s participation in the workforce (93).

ETHICAL ISSUES IN PERINATAL AND NEONATAL RESEARCH
The ethical conduct of clinical research involving children was recently reviewed by the Institute of Medicine in a report published in 2004 (94). Overall, the regulations (referred to as Subpart D) and the associated ethical framework are appropriate for research involving premature infants.

Although the topic is not unique to neonatology, several themes have been the subject of investigation and commentary in the context of neonatal research. These include (a) the prospect of direct benefit to an infant from being included in the research, apart from any direct benefit from the research intervention (95, 96); (b) the documented prevalence of the “off-label” use of medications and the need for evidence-based medicine (97, 98); and (c) the need for alternative approaches to the retrieval of informed consent for neonatal research (16, 99–101). These topics are not reviewed in this appendix. Specific questions arise, however, in two main areas: (a) the applicability of Subpart B at the threshold for viability and (b) the ability of adolescent pregnant women to consent to research. These two areas are discussed in more detail below.

**Applicability of Subpart B: Additional Protections for Pregnant Women, Human Fetuses, and Neonates Involved in Research**

Subpart B “applies to all research involving pregnant women, human fetuses, neonates of uncertain viability, or nonviable neonates” (102).

**Definitions**

“Nonviable neonate means a neonate after delivery that, although living, is not viable.”

“Viable, as it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration” (102).

**Research Involving Pregnant Women and Neonates**

Pregnant women or fetuses may be involved in research if all of the conditions that are listed in §46.204 are met. Consistent with the research protections found in Subpart A and applicable to all human research subjects, there should be sufficient preclinical and clinical data to assess “potential risks to pregnant women and fetuses.” Absent the prospect of direct benefit for either the pregnant woman or the fetus, the risk to the fetus must be minimal and the knowledge to be obtained must be important and unobtainable by any other means.

The definition of minimal risk is found in Subpart A: “Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”

“If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father’s consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.” Otherwise, the consent of the pregnant woman is sufficient. “For children as defined in §46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part.”

Children are defined as “persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.” There must be an independent assessment of the viability of the neonate. In addition, “individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.”
Neonates of uncertain viability and nonviable neonates may be involved in research (§46.205) if the following conditions are met: Neonates of uncertain viability may not be involved in research unless the research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or the purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research. If neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent’s legally authorized representative can be obtained.

After delivery a nonviable neonate may not be involved in research covered by this subpart unless all of the following additional conditions are met: (a) vital functions of the neonate will not be artificially maintained; (b) the research will not terminate the heartbeat or respiration of the neonate; (c) there will be no added risk to the neonate resulting from the research; (d) the purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and (e) the legally effective informed consent of both parents of the neonate is obtained (unless either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, or the consent of the father need not be obtained if the pregnancy resulted from rape or incest). The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice.

A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of subparts A and D of this part.

Go to:

**Research Involving Pregnant Adolescents**

Although the National Commission intended that the state consent laws for the treatment of minors apply in the research setting, this has been a point of contention and debate. For example, in adopting Subpart D, the Food and Drug Administration specifically did not adopt the waiver of parental permission found in 45 CFR 46.408(c) (103). “Section 46.408(c) of DHHS [U.S. Department of Health and Human Services] subpart D allows an IRB [institutional review board] to determine that a research protocol is designed for conditions or for a subject population for which the permission of parents or guardians is not a reasonable requirement to protect the subjects.” This section has often been used by institutional review boards to waive the requirement for parental permission for research involving adolescents, provided that the research involved procedures that the adolescent could consent to under applicable state law.

Although most states include marriage as a condition that results in the emancipation of an adolescent from parental control, only two states (New Jersey and Wisconsin) mention pregnancy or previous birth. The ability to independently consent for research participation as an “expanded” view of emancipation may be reasonable, but this has not been addressed explicitly in state laws (104).

State laws usually contain provisions for a minor to consent to health care (so-called mature minor statutes), with pregnancy often included as a qualifying condition. In addition, states allow a minor to consent to treatments for specific disorders or conditions such as sexually transmitted diseases, family planning, and alcohol or drug abuse. However, the applicability of these statutes to the research setting is far from clear (104).

**REFERENCES**


Footnotes

1

G. R. Baer, Department of Pediatrics, The Children's Hospital of Philadelphia and the University of Pennsylvania School of Medicine, Philadelphia. R. M. Nelson, Department of Pediatrics and Department of Anesthesiology and Critical Care, The Children's Hospital of Philadelphia and the University of Pennsylvania School of Medicine, Philadelphia.