Two-Year Neurodevelopmental Outcome of an Infant Born at 21 Weeks' 4 Days' Gestation

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Recent literature confirms that, at the lower limit of extrauterine survival, substantial intercenter variability exists in resuscitation practice. The reasons for this variability are unclear, but may be related to disagreement on how to apply the best interests standard to extremely premature infants. Currently, both obstetric and pediatric societies recommend against assessing for viability or attempting resuscitation before 22 weeks' gestation. In this context, we report the unimpaired 2-year outcome of a female infant resuscitated after delivery at 21 weeks' 4 days' gestation and 410 g birth weight. She may be the most premature known survivor to date. This infant had multiple risk factors for adverse outcome, including prolonged mechanical ventilation, bronchopulmonary dysplasia, and threshold retinopathy of prematurity. She achieved discharge from the hospital on low-flow oxygen at 39 weeks' 4 days' gestation and 2519 g. At 24 months' and 8 days' chronological age, she achieved cognitive, motor, and language Bayley III scores of 90, 89, and 88, equivalent to 105, 100, and 103 at 20 months 2 days corrected age. It is known that active intervention policies at 22 weeks' gestation improves the outcome for those infants and it may be reasonable to infer that these benefits would extend, if to a lesser degree, into the 21st week. Ultimately, such limited data exist at this gestational age that the time may have arrived for obstetrical centers to begin systematically reporting fetal outcomes in the 21st week.

Over time, advances in neonatal care have led to a gradual lowering in the gestational limits of survivability.[1] Recent literature confirms that, at the lower limit of extrauterine survival, substantial intercenter variability exists in resuscitation practices.[2] For infants delivered at 22 to 23 weeks' gestation, the variability in active treatment policies at delivery accounts for 75% of the variation in survival without severe impairment.[2] Further, of infants born at 22 weeks who received active intervention, 23% survived and two-thirds of survivors did not have severe neurodevelopmental impairment.[2]

The reasons for the wide variability in management practices are not entirely clear. Recent survey data suggest that US neonatologists split evenly between viewing the best interests standard as considering only the infant's well-being versus viewing the interests of the infant and the family being inextricably linked because negative effects on the family in turn are harmful to the infant.[3] This appears to be a shift in comparison with survey data from almost 30 years ago[4] when neonatologists largely agreed that parental wishes would influence their decision-making.

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Dr Ahmad conceptualized and designed the study, analyzed and interpreted data, and drafted the initial manuscript; Dr Placencia contributed to the initial manuscript draft and critically reviewed and revised the manuscript; Drs Fierro and Kenton and Ms Frey analyzed and interpreted data and critically reviewed and revised the manuscript; and all authors approved the final manuscript as written.

DOI: https://doi.org/10.1542/peds.2017-0103

Accepted for publication Mar 9, 2017

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

To cite: Ahmad KA, Frey CS, Fierro MA, et al. Two-Year Neurodevelopmental Outcome of an Infant Born at 21 Weeks' 4 Days' Gestation. *Pediatrics.* 2017;140(6):e20170103

TABLE 1 Bayley III Examination Results Corrected and Uncorrected for Prematurity

		Age-Equivalent, mo	Composite Score		95% Confidence Interval		Percentile Rank	
			Corrected	Uncorrected	Corrected	Uncorrected	Corrected	Uncorrected
Cognitive	Composite	21	105	90	97–113	83–99	63	25
Language	Receptive	19						
Language	Expressive	20						
Language	Composite		100	89	93–107	83–97	50	23
Motor	Fine	20						
Motor	Gross	21						
Motor	Composite		103	88	95–110	91–97	58	21

Currently, both obstetric and pediatric societies recommend against assessing for viability or attempting resuscitation before 22 weeks' gestation.[5,6] Further, we are unware of any hospitals with a policy for active resuscitation in the 21st week. This has resulted in a dearth of data examining the outcomes of infants born alive within the 21st week. In this context, we report the outcome of a female infant born at 21 weeks' 4 days' gestation whom we believe to be the most premature survivor reported.[7] She is now 2 years old.

CASE REPORT

This infant was born in San Antonio, TX, in 2014 to a 32-year-old $Gravida_6Para_1Abortus_4$ mother with early, regular prenatal care. We ascertained maturity by last menstrual period dating of 21 weeks 4 days, consistent with 9-week ultrasound dating of 21 weeks 2 days. The mother presented with preterm premature rupture of membranes for 80 hours, preterm labor, and chorioamnionitis. The infant was delivered through purulent amniotic fluid and her umbilical cord remained unclamped until initiating resuscitation 5 minutes after delivery at parental request, despite a lack of spontaneous activity. Her Apgar score was 6 at 10 minutes. Birth parameters included weight 410 g, head circumference 19 cm, and length 26 cm.

We initiated enteral feedings at 5 days of age with expressed breastmilk, after resolution of systemic hypotension. After 3 days of trophic feeds, the patient tolerated gradual increases in expressed breastmilk volume. We maintained an exclusive breastmilk diet, including fortification, for most of her hospital stay.

Our patient required 56 days of mechanical ventilation, including 31 days of high-frequency jet ventilation. Attempted extubation on days 3 and 49 failed. After successful extubation on day 56, she required 2 days of nasal prong ventilation and 47 days of high-flow nasal cannula. She received 108 days of systemic steroids (15 days of dexamethasone) and 93 days of hydrocortisone.

Serial echocardiography revealed a patent ductus arteriosus with a maximal size of 2 mm. Management consisted of mild long-term fluid restriction of 130 to 140 mL/kg per day total volume without pharmacological or surgical interventions. Repeat echocardiograms showed the patent ductus arteriosus to be small near discharge.

Bilateral threshold retinopathy of prematurity required intraocular bevacizumab therapy. Four neurosonograms and a 38-week brain MRI revealed no detectable abnormalities. Discharge support at 126 days after birth (39 weeks' 4 days' postmenstrual age) included 0.25 L per minute of oxygen, chlorothiazide, and inhaled beclomethasone. At discharge, the patient was successfully completing all feeds by mouth but undergrown: weight 2519 g (third percentile, *z* score −1.86), head circumference 31 cm (first percentile, *z* score −2.51), and length 42 cm (<first percentile, *z* score −3.50).[8]

At 24 months' 8 days' chronological age (20 months' 2 days' corrected age) the growth parameters with prematurity-corrected percentiles include a weight of 7.98 kg (<first percentile, *z* score −3.73), head circumference 45.2 cm (11th percentile, *z* score −1.24), and length 76.3 cm (fourth percentile, *z* score −1.77). Removing prematurity correction provides for a weight <first percentile (*z* score −4.53), head circumference fifth percentile (*z* score −1.62), and length <first percentile (*z* score −2.76).[9] The concurrent Bayley III examination demonstrated unimpaired developmental scores for age (Table 1). Further, the patient did not develop cerebral palsy, visual impairment, or auditory impairment.

DISCUSSION

Accurate assignment of gestational age has importance for research and public health purposes. In this case we do not have an assisted reproductive technology–derived gestational age. However, the presence of 9-week ultrasound dating only 2 days discrepant with last menstrual period dating meets criteria for best obstetric

estimate as outlined in recent recommendations.[10]

Many risk factors in this clinical vignette have an association with adverse neurodevelopmental outcomes. Despite these risks, the patient had unimpaired 2-year Bayley scores. Currently, both obstetric and pediatric societies recommend against assessing for viability or attempting resuscitation before 22 weeks' gestation.[5,6] Therefore, the lack of data on the outcomes of infants born during the 21st week of gestation is unsurprising. What is known is that active intervention at 22 weeks' gestation significantly improves the outcome for those infants.[2] It may be reasonable to consider that these benefits would extend, if to a lesser degree, to the 21st week. Further, the inconsistent application of core terms, such as stillbirth, influences clinical decisions in a way that adversely affects the potential for survival.[11] At the moment we initiated resuscitation, this infant would generally have been considered stillborn or an early postnatal death, had further assessment or intervention been withheld.

The outcome of this case raises many ethical questions. This intact survival of an infant delivered halfway through the 21st week may be considered both by obstetricians evaluating their approach to counseling and management of pregnancies, as well as by neonatologists approaching prenatal discussions and delivery room management of these patients. Clearly, 1 positive data point is insufficient to recommend aggressive obstetric and neonatal management of other 21-week pregnancies. However, neither may we ignore outcomes data solely because they do not fit comfortably into established practice. A useful approach to the questions raised by this case is to use the model established by Chervenak and McCullough.[12] This model provides a framework for how to balance beneficence- and autonomy-based obligations to the pregnant woman with beneficence-based obligations to the fetus, while also recognizing the pregnant woman's beneficence-based obligations to her fetus.

The obstetric team has autonomy-based obligations to inform the pregnant woman of the predicted outcomes associated with either aggressive or nonaggressive obstetric management for her and her fetus at 21 weeks. With the aggressive medical care provided to this infant, we can no longer say that mortality is certain at 21 weeks' gestation, though it remains highly probable. Similarly, the neonatal team should discuss the outcomes associated with aggressive neonatal management as well as the near certainty of death if a palliative care approach is taken. This information must be presented in a comprehensible manner to fulfill the autonomy-based obligation to the pregnant woman.

For beneficence-based obligations toward the fetus to exist, the health care team must both consider the fetus a patient and there must exist medical interventions that are reliably expected to result in a greater balance of clinical goods over harms. However, 2 inherent quandaries should be addressed. First, defining what is considered a clinical "good" versus "harm" requires dialogue between the medical team and the pregnant woman. It must be understood that what qualifies as a "good" or "harm" for 1 situation may not qualify in another, and also that parents and clinicians may differ on the definitions of these terms.[13] Second, we should recognize the paucity of reliable data to guide our clinical decision-making. Therefore, beneficence-based obligations to the fetus are weak and likely subordinate to the obligations toward the pregnant woman.

The beneficence-based obligations on the part of the pregnant woman to her fetus should be similarly analyzed. The pregnant woman is expected to take reasonable risks to her health for the benefit of the fetus, including, but not limited to, cesarean delivery. However, as with the team's beneficence-based obligations to the fetus, the mother's obligations are contingent on a reliable expectation of benefit. In the absence of clear benefit, the mother's obligations to her fetus are also weak. Therefore, any decisions regarding obstetric management rest primarily on the health care team's autonomy- and beneficience-based obligations to the mother.

Once the infant is born, health care decisions regarding the infant are entirely beneficence-based. The health care team and the parents should engage in shared decision-making focused on protecting the best interests of the infant, including the effects on the family, inasmuch as these effects in turn harm the infant.[3] Critical in guiding these decisions are population-based data that reflect the clinical condition of the infant and the infant's unique clinical circumstances. The implication is that should the infant survive resuscitation in the delivery room and appear stable in the early period, the health care team should continue to provide appropriate life-sustaining care. However, if the infant shows signs that life-sustaining care is no longer beneficial, the health care team should consider quickly pivoting toward palliative care.

Our management of this patient is consistent with this approach. Similar to the management approach now recommended by the American Academy of Pediatrics,[6] we initially counseled the mother against resuscitation in the delivery room, reflecting a weak beneficence-based obligation to the fetus. However, on the explicit request of the mother, we initiated resuscitation

of the infant. After showing signs of viability, we then proceeded to full life-sustaining measures. We felt justified in doing so because our beneficence-based obligation to the infant now tilted toward aggressive care due to the infant's vigorousness and the mother's assessment that a trial of intensive care best served her infant's interest. Although our patient experienced a prolonged hospital course, at no time did our continual reassessments of her condition change the conclusion that continued life-sustaining treatment was in her best interests.

Recent editorials have emphasized that gestational age–based resuscitation policies may not just reflect known, yet outdated, information but may also be adversely shaping those outcomes.[14] Indeed, it seems clear that outcomes at the lowest gestational ages can improve only if clinical practice continues to evolve.[14] Given the beneficial impact of active intervention at 22 weeks[2] and this report, the time may have arrived for obstetric centers to begin systematically reporting outcomes data for fetuses delivered within the 21st week of gestation, including the rates of liveborn versus stillborn. These data are necessary to guide adequate decision-making for these infants and are currently lacking.

ACKNOWLEDGMENTS

We thank Drs Veeral Tolia and Reese Clark for their critical review of this manuscript.

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