

What If the Prenatal Diagnosis of a Lethal Anomaly Turns Out to Be Wrong?

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Advances in prenatal diagnosis create a unique set of clinical ethics dilemmas. Doctors routinely obtain genetic screening, radiologic images, and biophysical profiling. These allow more accurate diagnosis and prognosis than has ever before been possible. However, they also reveal a wider range of disease manifestations than were apparent when prenatal diagnosis was less sophisticated. Sometimes, the best estimates of prognosis turn out to be wrong. The infant's symptoms may be less severe or more severe than anticipated based on prenatal assessment. We present a case in which a prenatal diagnosis was made of severe osteogenesis imperfecta, leading to a decision to induce delivery at 31 weeks. On postnatal evaluation, the infant's disease did not appear to be as bad as had been anticipated. We discuss the ethical implications of such diagnostic and prognostic errors.

As a result of advances in prenatal diagnosis, doctors can now conduct a much more sophisticated and precise diagnostic and prognostic evaluation of the fetus than has ever been possible before. Genetic screening, radiologic imaging, and biophysical profiling generate information that can inform discussions with parents about both prenatal and postnatal medical management. But sometimes, prenatal evaluation leads to expectations that are not confirmed on postnatal evaluation. Usually, this is not the result of a completely mistaken diagnosis. Instead, it is because many diseases manifest across a range of specific findings and may be less severe, or more severe, than anticipated. We present a case in which a prenatal diagnosis was made of severe osteogenesis imperfecta (OI), leading to a decision to induce delivery at 31 weeks. On postnatal evaluation, the infant's disease did not appear to be as bad as had been anticipated. We present comments

from the treatment team and 2 experts in pediatric palliative care.

CASE PRESENTATION

During routine midtrimester ultrasound screening, the fetus of a 21-year-old primigravida was diagnosed with a severe skeletal malformation. In the following days, amniocentesis and serial ultrasound examinations were performed to establish the exact diagnosis. At 30 weeks of gestation, severe OI was diagnosed. The identified point mutation "c.3008G>a, p.Gly1003Asp" in the Col1A2 gene had been previously associated with OI type II: the so-called "perinatal-lethal" type.¹ Evidence of thoracic hypoplasia, decreased bone density of the cranium, and multiple intrauterine bone fractures supported this diagnosis of a very severe and most likely "lethal" type of OI.

Parents had been involved in all stages of the diagnostic process and

abstract

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appeared to be highly committed to care for their infant irrespective of any anticipated health disorders. However, being faced with a disease that was considered “lethal,” the mother felt incapable of continuing her pregnancy. She was horrified by the idea that her infant suffered from fractures in utero and then subsequently died around or shortly after birth. On the other hand, feticide was out of question for both parents. An ethics consultation with participation of obstetricians and neonatologists was held. Mothers’ and child’s best interests were balanced and a medical induction of labor and primary palliative care of the infant was considered an acceptable therapeutic approach.

At 31+0 weeks of gestation, a male preterm infant was delivered vaginally from a breech position. His birth weight was 1170 g. Under close observation of the neonatal team, the boy was given to mother’s breast immediately after birth. His respiratory adaptation was uneventful without any medical intervention. No signs of discomfort were observed. After a while, he was placed in an incubator and after another while he was transferred to the neonatal unit where intravenous fluids were administered. He was eupneic and breathing in room air. His parents asked that his do not resuscitate order be cancelled and that he be given life-prolonging treatment.

The next day, an ethics consultation was summoned as the medical team was uncertain whether it should continue palliative care.

The Treatment Team Comments

OI is a genetic disorder with a prevalence of ~1:20 000. It is characterized by a distinct predisposition to multiple bone fractures and can be diagnosed in utero at the end of the first trimester.^{2,3} Ultrasonography findings of multiple fractures, bone demineralization, and shortening

and deformity of the long bones have been used to distinguish the “lethal” OI type II from other forms of OI and other skeletal disorders.^{4,5} But this way of differentiating “lethal” from milder forms of OI is deeply flawed. OI subtypes were developed by using retrospective data such as radiograph findings, genetics, and clinical course. By these criteria, OI type II was diagnosed when the affected individual had died in utero or shortly after birth. The criteria were not developed to be predictive. The sensitivity or specificity of different findings as predictors of prognosis has never been validated. Nevertheless, these categories are still used and type II is considered the most severe type.

A significant limitation of these diagnostic and prognostic criteria is that they were developed without taking into account the effect of medical interventions. A recent review stated that OI “type II is lethal, usually because of respiratory failure resulting from multiple rib fractures.”⁶ This is the case only if one decides not to treat respiratory failure due to rib fractures.

We did not find any respective study that was not biased by self-fulfilling prophecy or patient selection. In one retrospective study of “lethal” congenital anomalies, approximately three-quarters of pregnancies were terminated and 90% of the live-born infants died before 4 months of age. When the diagnosis was made prenatally, the infants received less intensive care compared with those who were diagnosed postnatally. Because aggressive treatment was not associated with prolonged survival, the authors concluded that it should not be offered.⁷ This is a classic self-fulfilling prophecy. It is hard to know what the mortality rate would be with treatment if current outcome statistics are based on cohorts in which many affected infants die after termination of pregnancy and another large number

of infants receive palliative care after birth.^{8,9} We believe that classification is not useful today and that the spectrum of clinical severity of OI should be considered as continuous rather than classified into discrete categories.

With an explicit aim of preventing early postnatal death, the treatment of respiratory failure due to rib fractures is likely to be effective. However, death also may result from an undersized thorax, overall thoracic wall instability, and pulmonary hypoplasia.¹⁰ When such features are present, they are likely to be associated with high mortality, even with treatment.

Genetic results are also problematic. OI is a highly heterogeneous disorder in which no reliable genotype-phenotype correlation exists.^{11,12} Nevertheless, in cases of diagnostic uncertainty, clinicians and especially parents might be tempted to attach high importance to a distinctive and verifiable genetic feature. In any case, parents should be counseled carefully and the limitations of genetic test results should be discussed in detail.

The most influential problem is not specific to OI. It arises with the concept of “lethal” congenital malformations. The term “lethal” is very imprecise.¹³ However, a common understanding is that a “lethal” diagnosis implies an irresistible progression of a disease that inevitably leads to death in the near future.¹⁴ Such understanding and usage of the terminology “lethal” unavoidably implicates that treatment of such a condition is futile or even detrimental. As reported previously and now observed in our case, such “lethal” language predetermines medical treatment, because it predetermines parental and medical anticipations on the clinical course.¹⁵ “Lethal” language is harmful because it may distract parents from unprejudiced decisions between different treatment options. When counseling in cases

of life-threatening fetal anomalies, most physicians encourage a certain treatment option. Furthermore, significant discrepancies in counseling can be observed depending on whether a condition is considered to be “uniformly lethal” or “uniformly severe, commonly lethal.” Because of the inherent ambiguity in such terms, we recommend physicians to avoid the term “lethal” in communication practice and, even more importantly, in the nomenclature of diseases.

With these considerations in mind, we can examine the 3 options that were offered in this case at the time of the prenatal ethics consultation: (1) carrying the child to full term and perinatal palliative care, (2) feticide and termination of pregnancy, and, because the mother had already rejected these options, (3) medical induction of labor and perinatal palliative care. Active intervention by means of full intensive care was not discussed as a treatment option. Although options (1) and (2) were identified as ethically most consistent due to their clear consequential effectuation of an either mother-centered or child-centered perspective, option (3) was finally considered acceptable, although concerns had been raised that this approach might imply therapeutic disadvantages to the infant and neglect potential harm for the mother at the same time. This may seem like the worst of both worlds. We disagree.

In a case like this, it is permissible to allow the mother to take some risks as long as she understands those risks and they are consistent with her overall goals. Many parents want to see and hold their living infant, even if that infant is not likely to survive. In such situations, both aggressive and nonaggressive intrapartum monitoring should be considered, depending on parents’ preferences. Parents and health care professionals should be prepared for a situation

in which an infant with a life-threatening congenital malformation will not die immediately after birth but will survive for days or more.^{16, 17} Significant outcome-relevant discrepancies between the proposed prenatal and the actual postnatal diagnosis may occur.

One should also bear in mind that palliative care does not per se limit certain interventions. An infant with a severe congenital OI might have difficulties in respiratory adaptation like any other nonaffected infant. So there might be a palliative indication to give supplemental oxygen in such a case or even to give some additional respiratory support if there is a reasonable prospect that the infant can overcome this temporary disturbance. In a pre- as well as a postnatal setting of a severe congenital malformation, the consideration of all possible treatment options and respectful communication with the (future) parents are essential prerequisites to respect parental autonomy and to ascertain the child’s and families’ best interests. Especially when decision-making is informed by prognostic concepts, the narrative co-construction and negotiation of therapeutic goals and strategies between health care professionals and parents and thus the influence of subjective values and judgments must be taken in account.

In this case, we decided to forego palliative care and to start full life-sustaining treatment. The parents were fully aware of the anticipated outcome of an infant with severe OI. However, their decision to ask for termination of pregnancy and palliative care was likely based on the assumption that their infant would suffer and die shortly after birth. We were wondering why the outcome of our prenatal assessment was that inaccurate and we are now convinced that the use of the term “lethal” distracted the parents and

the clinicians from an unprejudiced assessment of the survival prognosis.

Jenni Linebarger, MD, Pediatric Palliative Care Physician, Comments

Perinatal diagnosis comes with inherent uncertainty. Providers rely on imaging, genetic studies, and experience (personal and published) to formulate a prognosis before they can truly “see” the infant. As such, planning for care at delivery often follows the mindset of “prepare for the worst, hope for the best.” In this case, the providers and the parents prepared for the infant’s death based on the genetic diagnosis of OI type II and the thoracic hypoplasia noted on ultrasound. Yet on day of life 1, the infant is eupneic and breathing in room air, leaving the providers uncertain about how to proceed and doubting whether to continue palliative care.

Of course you provide palliative care!

Palliative care is not exclusive to the end of life. Palliative care is provided for patients with a wide range of life-limiting and life-threatening conditions; ideally beginning when an illness is diagnosed and continuing regardless of whether a child receives treatment directed at a cure or prolonging life. The role of palliative care is to address physical, psychological, and social stressors, with a focus on improving the quality of life.

The infant boy in this case has genetically confirmed OI, and as the OI Foundation Web site states, “There is no cure for OI, but there are ways to manage the symptoms.” So in one sense, all treatments for patients with OI are “palliative,” not meant to cure, but meant to manage. For patients with OI type II (and severe type III), the life expectancy is shortened. Although the infant boy in this case appears to be breathing well now, we do not know whether that will continue over time. Given such remaining uncertainty, a palliative care team may aid the parents and

the treatment team in outlining goals for this infant's care.

The parents in this case have been given the gift of time with their son that they did not anticipate. How do they want to fill it? Using a 4-quadrant decision-making tool may help the family outline the goals for their son's care by taking into account their values as well as the medical indications (diagnosis, symptoms, proposed interventions), the infant's current and anticipated quality of life (important activities), and contextual issues that make up the nonmedical side of life. It may be, for example, that an isolette and intravenous fluids do not fit into their goals, and that they would prefer to have him room-in and breastfeed ad libitum.

Prenatal palliative care teams are familiar with infants who are delivered and do better than expected, as well as infants who do worse. In such cases, it is crucial to talk to parents about uncertainties and about their hopes, fears, goals, and plans. In this case, they have been given the gift of time with their infant. We should help them figure out how to best appreciate and use that gift.

**Jennifer K. Walter, MD, PhD, MS,
Pediatric Palliative Care Physician
and Clinical Ethicist, Comments**

Pediatric patients with serious illness sometimes defy expectations when technologic support is withheld or withdrawn, doing better than anticipated. In such cases, clinicians should explore 3 different potential areas of concern: the facts of the diagnosis and prognosis, the values and goals of care of the family, and the overall experience of how to partner with families given uncertainty. In doing so, clinical teams can help families determine a plan of care consistent with their goals for their child.

In this case, let's first focus on the diagnostic and prognostic "facts"

and uncertainties. Prenatal genetic testing has identified a "lethal" type of OI. Infants with this genetic syndrome often do not survive to birth and usually die in the first 2 months, but others may live until 1 year of age, usually dying of respiratory infections and insufficiency.¹⁸ The parents and team chose to induce preterm labor due to a concern that the infant would suffer significantly in utero and after birth. However, after delivery, the child was found to be comfortable: not demonstrating signs of significant pain from fractures, able to breathe without support, and interested in feeding (although it would be unusual for a 31-weeker to adequately feed without help given his gestational age).

The child's healthy appearance at birth raised questions about the accuracy of the prenatal genetic testing. Although there is growing evidence that the phenotype-genotype correlation is accurate for the gene mutations found,¹⁹ the child's condition could reasonably lead the team and parents to question the veracity of the diagnosis. Confirmation of the diagnosis with other physical examination findings by geneticists, and even repeat genetic testing, would not be unreasonable while acknowledging that the diagnosis is most likely accurate.

Although the exact progression of this child's disease is unknown, his trajectory is very likely to worsen in the coming months, with increasing fractures requiring pain management and the need to balance comfort with respiratory insufficiency. All prognostication about what to expect should be underscored with uncertainty because he could decompensate at any point. Many children with OI type II will also suffer from pneumonias and a progressive need for positive pressure ventilation, which can be painful due to mask

interfaces that result in further fractures. Preparing families for these declines and helping them recognize that regardless of the choice now, there may be a time in the near future where the burdens of interventions such as intubation, continuous positive airway pressure, or maintaining wakefulness in light of difficult pain management may warrant a primarily comfort-focused approach with little or no respiratory support.

Second, let's turn from facts to consider values and goals of care. Although the diagnosis is being confirmed and the prognostic range clarified, the medical team should revisit the values of the parents. In the case we learn that the parents are "highly committed to care for their infant" irrespective of the disorder he may have, yet also want to protect him from suffering. Coupled with the child's unexpected condition at birth, the clinical team then questioned whether palliative care was still warranted, even if the genetic diagnosis was correct.

Pediatric palliative care is often described as an extra layer of support in decision-making and symptom management for children with serious illness, often provided in conjunction with life-prolonging treatments. The team and family do not need to make an either-or decision. In fact, the clinical team may have been asking whether they should continue to recommend a primarily comfort-focused approach given the child's well appearance and likely need for support in feeding with a nasogastric tube (NGT).

So how should the team weigh whether a comfort-only approach is warranted given the parents' wishes to care for their child while also preventing suffering? Given the possibility that this infant would live longer with some life-sustaining treatments, such as artificial nutrition, and at some point in the future, will likely need noninvasive

or invasive respiratory support, the team must consider whether withholding these treatments now is ethically acceptable. Some clinicians are reluctant to start any life-sustaining therapy given the potential psychological challenge of withdrawing it in the future. That is generally not the best approach. When it is ethical to withhold a treatment, it is generally also ethical to withdraw that treatment.²⁰

The team and family should consider what is in the best interest of this child from the child's perspective, while weighing the risks of each possible intervention. For example, providing the child with supplemental nutrition by NGT carries low risk with the potential benefit of extending his currently good quality of life, one that does not include intractable pain or repeated interventions. The clinical team should reengage the parents, discuss the realities of the infant's current good status, and recommend NGT placement with supplemental feeds to offer him the possibility of extending his life, and keeping him from feeling hungry, as long as he maintains a good quality of life.

In making this first recommendation for NGT feeding, the care team must further explore the family's values and assess the level of suffering that they are willing to tolerate for their child in the future to potentially prolong his life. The team should also recommend home hospice services, given the dynamic nature of the child's disease. Concurrent care insurance legislation has meant that hospice can frequently be offered simultaneously with life-sustaining treatments for these types of patients.

Third, let's consider how we can partner in the face of uncertainty. Parents who have struggled to make a decision to withhold or withdraw life-sustaining treatments may experience increasing distress when their child appears to be doing

better than expected. Therefore, the uncertainty regarding possible outcomes should be part of the discussion of any decision to limit interventions. Clinical teams can anticipate potential scenarios in advance and agree on the kinds of interventions that they would be willing to offer to families given the clear expression of their goals.

Primary clinical teams, working with pediatric palliative care specialists and ethics consultants, can successfully navigate these discussions by recognizing their role in supporting the decision-making of parents, learning what is most important to families, and then making recommendations that are consistent with those goals and values. Merely offering families a menu of options can be overwhelming and unfair given our professional responsibility to guide families through these difficult decisions. With careful coordination of care and clear communication, teams can help families realize their hopes for a comfortable quality of life, or a peaceful death, for their child.

John D. Lantos, MD, Comments

This case illustrates the challenges that pediatricians face as a result of new technologies for prenatal diagnosis. Although we can get much more information about the health and well-being of a fetus than ever before, the wealth of new information may be difficult to interpret. Statisticians and epidemiologists have long known that the availability of more tests does not necessarily increase the precision or the accuracy of diagnosis. Instead, more testing may lead to more uncertainty. This can happen when tests give conflicting results or when tests are used in populations for which their sensitivity and specificity have not been evaluated.²¹ Paradoxically, more information can lead to less certainty. Recognition of these

problems should lead to special caution in discussing the results of prenatal evaluations. There should always be a caveat about confirming the prenatal findings on postnatal evaluation.

ABBREVIATIONS

NGT: nasogastric tube
OI: osteogenesis imperfecta

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