Challenges of Uncertainty in Prenatal Decision-Making: Skeletal Dysplasias

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Abstract: When skeletal dysplasias are suspected in the prenatal period, investigation, counseling, and management become especially challenging. By better understanding the complex forces at play and parental values, prenatal health care providers may improve the ways in which they counsel patients to improve the decision-making process under conditions of significant uncertainty, including in cases of prenatally suspected skeletal dysplasia.

Prenatal suspicion of skeletal dysplasias (SDs) presents challenges in investigation, counseling and management. SDs are a heterogenous group of over 400 genetic disorders of development, growth and maintenance of the human skeleton.[1] These lie on a spectrum of severity, ranging from minor disabilities and short stature to significant physical and developmental impairments.[2] In this manuscript, we define life-limiting SDs as SDs that result in neonatal or early infant death due to adverse effects on lung development.[3] The combination of expected shortened lifespan, concerns about suffering, and potentially lower quality of life (QOL) may negatively impact prognosis.[4] Physicians therefore usually offer different care options following investigation, including pregnancy termination, neonatal palliative care, or neonatal resuscitation.

In this paper, we focus on prenatally suspected SDs based on ultrasound findings. We argue that SDs exemplify particularly challenging clinical and ethical circumstances, including: (1) later diagnosis in pregnancy; (2) diagnostic and prognostic uncertainty; (3) lack of fixability, in terms of availability of cure or surgical "fix"; and (4) overt physical disfigurations and disability in many cases. The problem of significant uncertainty underlies these epistemic difficulties. Although there are many clinical conditions that have some of these components, conditions that have all of these components are less common. Prenatally suspected SDs thus serve as a case study to underscore the ways in which clinicians often inadequately acknowledge and address uncertainty in prenatal counseling and management.

Clinical uncertainty and provider biases may obscure recommendations regarding the best course of action, including decisions around prenatal testing and termination. We explore the normative ethi-

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cal factors that influence parental decision-making in cases of severely life-limiting prenatal diagnoses. By understanding these complexities, health care providers (HCPs) may clarify and improve the decision-making process in the context of significant clinical uncertainty. Awareness of current perceptions and biases may lead to insights that ensure equitable treatment, allowing for conscious course-correction in counseling and management.

The Case

A healthy pregnant woman discovers that her fetus has severely shortened, bowed femurs at her 19-week anatomy ultrasound. Two weeks later, all long bones appear short and the cranium abnormally shaped. The chest seems significantly smaller than expected, leading to counseling about highly likely "lethal" SD.[5]

There is no family history of SDs. A geneticist describes the possibility of a "lethal" SD. The patient declines invasive prenatal testing and termination, accepting referral to perinatal hospice instead. Third-trimester ultrasound reassessment of possible head abnormalities is less pronounced, and chest size and interval fetal growth appear relatively appropriate, despite short long bones. The patient decides against neonatal palliative care, opting for life-sustaining medical interventions if needed.

The patient delivers at term. The female newborn requires respiratory resuscitation shortly after birth. Physical features include bowing deformities of the legs, prominent eyes, blue sclera, and low-set ears. X-rays show evidence of in-utero long-bone fractures. These are consistent with a clinical diagnosis of severe osteogenesis imperfecta, confirmed with genetic testing. Following hospital care and initial medical treatment with intravenous zoledronic acid,[6] the infant is discharged home, with planned follow-up in a pediatric metabolic bone clinic.

Diagnostic & Prognostic Challenges of Skeletal Dysplasias

This case demonstrates the inherent diagnostic and prognostic challenges of SDs, especially when suspected on fetal ultrasound. For those that present with prenatal signs, confirmation of the diagnosis often occurs later in pregnancy. Balancing the risks of invasive prenatal genetic testing against the anticipated utility of information obtained is another challenge. Although the risk of miscarriage with amniocentesis is less than 0.5%, and is about 0.5% with chorionic villous sampling,[7] women may decide against these procedures if diagnosis will not alter their decision to continue the pregnancy.

For those who do pursue these tests, the results may not provide the answers that matter to them most: Will my baby survive? Will he or she have disabilities and if so, exactly what kind and how bad will they be? Can he or she grow up to be healthy and, if not, how will that impact the ability to go to school, make friends and lead a full and happy life? How will the child's condition affect the entire family?

Significant progress has been made in molecular prenatal diagnosis through the use of next-generation sequencing technologies that allow earlier, more rapid, and accurate genetic testing, especially for some life-limiting SDs, such as thanatophoric dysplasia.[8] Rapid prenatal diagnosis with next-generation sequencing may certainly be helpful for prenatal counseling and pregnancy management. Studies acknowledge the clinical heterogeneity of SDs,[9] but unfortunately, even rapid prenatal genetic diagnoses are limited regarding the persistence of uncertainty around the resulting postnatal phenotype (clinical manifestation of the genetically diagnosed condition).

There continues to be an overestimation of the degree to which phenotype can be predicted,[10] even in the absence of studies that follow the clinical cases over a period of years. Longitudinal studies may answer some of the long-term questions parents have about neurodevelopmental outcomes, extent of disability, QOL, and the degree of clinical variation expected for any particular genotype. Correlation between the genetic diagnosis (genotype) and the phenotype severity, though improved, remains inadequate for many other SDs, including osteogenesis imperfecta.[11] To the chagrin of both clinicians and patients, prognostic uncertainty often persists despite prenatal diagnosis.

Since genetic testing for SDs may not predict clinical severity, many women choose to avoid the risks of prenatal testing in favor of postnatal investigation. A fetus diagnosed with a life-limiting SD may be stillborn, while another fetus with the same diagnosis might be liveborn and survive for hours, days, or even decades. Milder SDs may not be diagnosed prenatally at all. Willingness to undergo invasive prenatal testing often depends on gestational age,[12] with greater hesitancy closer to viability. Timing of prenatal testing for SDs becomes critical with regard to what options may be offered depending on gestational age limitations for termination in different jurisdictions.[13] Although most life-limiting cases are suspected at the second trimester anatomy ultrasound, with the finding of shortened long bones,[14] the indicators associated with severely life-limiting SDs may only become evident on subsequent ultrasounds. Ultrasound indicators suggesting greater disease severity include small bell-shaped

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chest (associated with poor lung development and greater risk of respiratory failure after birth),[15] evidence of low-density bones in the fetal skeleton, and hydrops (fetal heart failure).[16] Experts do not agree on which marker best predicts severity.

The perception of lethality (a term we prefer to avoid) depends on advances in medical technology, and subjective value judgments about disability and QOL.[17] Lethality also often involves the bias of self-fulfilling prophecy,[18] where historical experience with a life-threatening condition leads clinicians to recommend no life-sustaining interventions, based on notions of futility, leading to earlier death, rather than death due to the disease. Uncertainty around the duration of survival may have variable significance for parental decision-making.[19]

The broad clinical spectrum of SDs may lead to greater uncertainty regarding suffering, extent of disability, and QOL for the patient and family. Other congenital anomalies, such as spine and heart defects, also have variable clinical presentations, but factors such as size, location or other associated ultrasound findings narrow the differential diagnosis, predict clinical symptoms and severity, and direct opportunities for intervention with greater accuracy. Association of these other anomalies with genetic or chromosomal abnormalities often portends a poorer prognosis.

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"Fixability" and Quality-of-Life Concerns

Musculoskeletal abnormalities and associated disabilities, such as short stature, limited mobility and need for a wheelchair, are more overtly visible, compared with malformations such as congenital heart or kidney disease. HCPs' attitudes towards disability may be mediated by socially prevalent attitudes and biases around the aesthetics of disability. These involve negative reactions to visible signs and behaviors seen with disability, triggering subconscious prejudices based on fear and disgust, which are "involuntary, visceral reactions based on deeper collective norms of beauty."[23] These subconscious biases have the capacity to "undermine even the most intellectually enlightened and well-intentioned" people.[24] Importantly, as can often be the case with SDs and other disabling conditions, the extent of disability is not necessarily apparent at the outset. If the clinical manifestations of disease are uncertain, then their impacts on individual appearance and function are also uncertain. Biases against disability may lead to assumptions about the extent to which significant disability may be a prominent feature of an individual's life, despite the uncertain reality of what degree of disability may actually require accommodation.

Medical innovations that improve outcomes and longevity for other congenital anomalies have not been developed to the same extent for SDs. Fetal surgery can be performed for spina bifida to improve mobility and reduce the need for shunts in childhood.[25] Cases of hypoplastic left heart syndrome may be treated in-utero to improve survival.[26] Fetal procedures are not necessarily curative, but the ability to intervene prenatally to improve outcomes may result in more optimistic attitudes. Although some types of SDs are amenable to surgery, the overall lack of fixability in the form of procedures that dramatically improve outcomes and visibility of anomalies may affect HCP attitudes and subsequent management options offered or emphasized, including termination.

HCPs have varying opinions regarding termination at different gestations, depending on the particular fetal anomaly.[27] Examination of the underlying motivations for defending termination for different anomalies showed that physicians tend to prioritize the professional values of fixing, minimizing pain and optimizing normality.[28] For example, clinicians did not support termination for cleft lip because it is easily

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repaired surgically in infancy, with no residual impact on QOL. In another study, 70% of pediatric cardiologists surveyed said they would seek legal action to mandate surgery when parents refuse it for congenital heart disease with < 5% mortality rates following surgical correction (i.e. fixable).[29] By contrast, clinicians showed significant support for termination in the context of conditions that could not be fixed, such as hypoplastic left heart syndrome, spina bifida and Trisomy 21,[30] and fewer than 10% of the cardiologists would seek legal action to mandate surgery in cardiac conditions with poor prognosis.[31] Some of the conditions, including many forms of spina bifida and Trisomy 21, are actually not considered life-limiting, although disability is often a common feature. This further supports the likelihood of clinician biases against overt disability, in addition to favoring fixable conditions. In these non-life-limiting cases, QOL concerns were raised by the clinicians for both the individual and the family.[32] This supports previous findings that suggest clinicians overemphasize the negative consequences and underestimate the potential for positive life experiences for individuals with disabilities and their families.[33]

While biases against disability may understate the uncertainty around a possibly *less* disabling outcome, biases towards fixability may overstate the extent to which certain conditions are truly fixable, where surgical intervention is possible. Of course, informed consent around possible surgical interventions involves a discussion of both risks and benefits with patients. However, according to a study of over 300 potential adult patients, there is an optimistic bias around fixability, tending to overestimate benefits and underestimate risks of medical interventions.[34] These results point to larger social biases towards cures, correction of abnormalities and eradication of imperfections and away from acceptance of "defects," more generally, rather than solely amongst clinicians. There is obvious value in treating pain and illness, but it does not necessarily follow that the persistence of disability leads to an unacceptable life of tragedy and suffering that is objectively undesirable.[35] These widespread assumptions reflect the extent to which these biases are socially pervasive and perhaps warrant challenging.

The social attitudes and clinical biases against overt disability and towards fixability both exacerbate and underscore underlying public and medical aversion to uncertainty — uncertain prognosis, uncertain degree of disfiguration, and the uncertainty of individual social and functional capacity — and its implications for QOL. Evidence regarding QOL as perceived by affected individuals with SDs and their families is lacking. One study comparing adults with short stature with and without SDs found that those with SDs experienced more daily pain, reduced physical abilities, fewer social supports, difficulties in accessing goods/services, reduced satisfaction with work and health/social services, and increased feelings of inequality.[36] The extent to which ease of accessibility and acceptance of disability are socially accommodated confounds these findings. The study did not address whether patient dissatisfaction mirrors many HCP perceptions of disability as unhealthy and missing out on a normal life experience.[37] A qualitative study of disability cultural competence amongst physicians found that most participating physicians defined disability based on medical status rather than recognizing the extent to which social factors contribute to disability.[38] Previous studies comparing perception of QOL by parents versus physicians (not specific to SDs) have shown that HCPs rank severe disability as having a more dismal impact on QOL than parents perceive.[39] HCPs should therefore be wary of their biases around QOL.

Challenges with the Decision-Making Process

Since the diagnosis of SD often occurs later in pregnancy, skeletal anomalies are a common cause for second- and third-trimester termination. Studies cite musculoskeletal abnormalities as one of the most frequent reasons for termination, comprising over 40% of cases.[40] Fetal structural malformations, including SDs, are the reason for over half of terminations after 32 weeks.[41] Several studies have shown that SDs consistently rank in the top three congenital malformations for second- and third-trimester terminations,[42] often related to later diagnosis and prognostic uncertainty.[43]

These studies do not examine why decisions were made to terminate for different anomalies, nor the differences in counseling. The extent to which SDs are treated differently is unclear. Many studies examine the experience of pregnant women with counseling for genetic anomalies. One showed that women are often dissatisfied with counseling outside of a specialized fetal medicine unit, experiencing anxiety, confusion, and unanswered questions.[44] Additionally, when pregnant women feel that they have not received adequate prenatal counseling prior to undergoing even non-invasive testing, they experience decisional regret (frustration, anxiety, and anger) upon receiving high-risk, incorrect, or inconclusive results.[45] Given the magnitude of diagnostic and prognostic uncertainty involved in cases of SD, it would not be surprising if pregnant women experienced similar frustrations with counseling.

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The frustration of patients who feel inadequately counselled may also relate to the lack of expert consensus. The diversity in professional perspectives may be due to the rarity, ambiguity and uncertainty around diagnosis and prognosis. The possibility of an evolving clinical picture that diverges from original expectations may also play a role in diverging expert opinions. The fact that there can be surprisingly better outcomes than expected in the face of an originally guarded prognosis in cases of SD may parallel that seen in cases of extreme prematurity, particularly in the periviable grey zone, where resuscitative measures may yield unexpected outcomes.[46] These aspects of clinical decision-making have not been examined much in the context of prenatal suspicion of SDs, but these clinical contexts share a similar degree of uncertainty.

Normative Ethical Considerations for Prenatal Decision-Making

By understanding the factors that influence parental decision-making, HCPs may better elicit their patients' values and counsel accordingly. Three main themes likely influence parents when they consider termination following the diagnosis of life-limiting or severely debilitating fetal anomalies: (1) "all life is precious," (2) "hope for a positive outcome," and (3) "a life worth living."[47] The first theme relates to parental notions of fetal worth and intrinsic value, through increased attachment and personification experienced with fetal movement, visualization with ultrasound, and personal beliefs. For other parents, this theme may relate to learning from past experiences and views of disability, and balancing parenthood with other life circumstances. The second theme reflects concerns regarding the parent's own imagined future, often influenced by anecdotal accounts of others, leading to either optimism or pessimism towards a single outcome. Hopefulness may actually represent false hope, based on incorrect assumptions or poor understanding of risk. The third theme describes parental considerations of QOL for the fetus, as well as responsibilities and commitments to other children, recognizing that decisions made affect the entire family.[48]

Although some SDs may be more clearly life-limiting, many are characterized by uncertainty at the various levels previously discussed. The three themes described above represent normative ethical considerations that would likely come into play to a similar degree for those SDs that have a narrower prognostic range, on the severe end of the spectrum. However, in the setting of a broad prognostic range, it is unclear how increasing degrees of uncertainty might adjust the weight given to these values. The degree of prognostic uncertainty may impact whether parents decide to pursue invasive prenatal testing and possible termination following prenatal diagnosis of SD. Optimistic parents may place greater value on hope for a positive outcome under conditions of uncertainty, whereas for others the presence of significant uncertainty along with a high aversion to the risk of a severely life-limiting SD may lead them to give greater weight to the considerations of a life worth living. These values affect decisions to pursue palliative care versus resuscitation. In addition to prognostic uncertainty and phenotypic variability, these decisions may be further complicated by the aforementioned insufficient knowledge about QOL, perceptions of a lack of fixability, and visible disability, inherent to SDs.

Receiving difficult prenatal diagnoses leads parents to combine new information with prior knowledge/beliefs about disability, as well as evaluate the certainty of the diagnosis, their own ability to parent a child with disability, the wider impact on others, and the availability of social supports. Parents often continue to have persistent hopes for the child to be born without the disorder, feeling guilty if they terminate the pregnancy.[49] For other women, choosing termination following prenatal diagnosis is accompanied by the belief that their decision appropriately considered the potential negative impact on QOL for the child, themselves and their families.[50]

Variability in risk aversion and tolerance of uncertainty will lead to different decisions. Some individuals seek to optimize the best possible outcomes, while others try to minimize the risk of worst possible outcomes.[51] Still others may make decisions based on minimizing their own regret — decisions with which they "can live,"[52] especially under conditions of ambiguity.[53] Regardless of whether they choose to continue or terminate pregnancy following diagnosis of fetal abnormalities, parents can experience grief, shock, disbelief, isolation, anger, and difficulties with adaptation.[54] With suspected SDs, they have to contend with an evolving clinical picture, where little may be known initially and the severity of the condition may only later become apparent. Sometimes a dire prognosis may be anticipated, but supportive treatment after birth may lead to surprisingly acceptable realities for patients and families.

Women often experience the larger social pressures to make choices that prove that they are worthy of motherhood, rather than asserting their decisional autonomy within a supportive social context.[55] These include decisions to proceed with as many prenatal tests as possible to mitigate any risk to the fetus or to terminate pregnancy, thereby eliminating the

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potential of any suffering and reduced QOL for the offspring. This may lead to psychological or moral distress following a decision with which the woman was not fully comfortable. A lack of understanding of the complex forces at play when it comes to patient decision-making may exacerbate the confusion, frustration, and uncertainty in a clinical context already fraught with unpredictability and bias.

Back to the Case: Supporting Decision-making in the Context of Significant Uncertainty

In the case presented, given the problems of diagnostic uncertainty and evolving clinical picture over the course of pregnancy with SDs, we can appreciate the conflicting ultrasound findings over time. Some clinicians seemed to convey more certainty than would have been warranted by suggesting that the fetus was highly likely to have a life-limiting SD. The full range of possible prognoses and the patient's interpretation of the working diagnosis were not fully explored. The woman was left with an (erroneous) understanding that the fetus was highly likely to die. This led to her accepting perinatal hospice referral, which was subsequently retracted when ultrasound findings appeared to show clinical improvement. When greater certainty is expressed than may be warranted, later revealed uncertainties may lead to a more traumatic patient experience. It can be distressing for parents to contend with the possibility of their newborn's death, only to discover that it is highly unlikely to occur. It is disconcerting that the possibility of survival with an unknown degree of disability was not discussed. This case might have been managed differently. In future cases, there is potential to better convey the uncertain and evolving nature of prenatally diagnosed SDs.

Firstly, there are a set of disclosures that should be made at the outset, including clearly acknowledging the degree of uncertainty that is present. HCPs influence parental prenatal decision-making with how they present risks, benefits, statistics and options, sometimes obfuscating the reality and extent of uncertainty present for a particular case. Some patients may perceive the "mere offer of a test… as a recommendation."[56] It is important for parents to understand that while prenatal diagnosis may inform further testing and preparation for potential outcomes, diagnosis alone cannot confirm prognosis. These nuances should be made clear to the individuals making these decisions, at the outset.

Secondly, patients need to know that the clinical picture may evolve over time and uncertainty often persists despite obtaining additional information. Decisions to proceed with a particular care plan may also change. A careful balance must be struck between non-directiveness, respect for patient autonomy,[57] and the provision of guidance by HCPs, based on their clinical knowledge and experience.[58] At the same time, since severity of prognosis may only be clarified later in pregnancy, patients who would consider termination should know that deferring decisions until they have more information might result in having to make those decisions in the second or even third trimester. In some cases, further information may only come to light postnatally.

Thirdly, adequate expert support throughout the process is important. Prenatal multidisciplinary meetings between geneticists, maternal-fetal medicine, and pediatric specialists are essential in providing context around SDs, revisiting priorities, and updating plans in the face of changing clinical circumstances. HCPs in these teams should also be aware of any implicit

SDs serve as a case study that incorporates the many layers of uncertainty involved in prenatal decision-making. The allusions made to other genetic conditions, birth defects, and extreme prematurity underscore some of the various ways in which these aspects of uncertainty, especially in terms of diagnosis and prognosis, often complicate high-risk pregnancies. Acknowledgement that unknowns often lie at the heart of challenging decisions may empower patients to accept the imperfections of the decision-making process, and to trust their choices despite the limited information available to them at the time of the decision.

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biases based on perceived cultural expectations or socioeconomic status that may be present.[59] Postnatal confirmation of the diagnosis, clinical and genetic assessment, as well as pediatric follow-up, should also be highlighted as an essential part of the evolving diagnostic and prognostic picture for parents continuing pregnancy.

Finally, support and respect for reasoned parental decisions are essential. Both patient and clinician perspectives should be sought, with sensitivity and care in the approach taken. Awareness and acknowledgement of clinicians' potential biases in counseling regarding conditions that rely on supportive rather than curative interventions, and the larger social and cultural pressures on mothers to minimize risk and disability for the offspring, may prove invaluable. It may be useful to elicit parental perceptions to better understand whether they are experiencing undue negative social pressure. The vague language of lethality should be avoided. Humility in approaching diagnosis and prognostication is warranted because prenatal diagnosis of a life-limiting SD can be incorrect — the child may only have mild symptoms later in life. Although there are limited population-level statistics, survival usually cannot be predicted for an individual case. In eliciting patient values and normative ethical considerations, HCPs might also discuss how parents feel about risk and uncertainty within the context of SDs. Such conversations may not necessarily lead to resolution or clarity regarding the best decision but may serve to highlight the various ways in which risk and uncertainty are perceived, and their impact on decision-making.

Conclusion

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