# Voices of experience in periviable decision-making and artificial placenta technology

Boer, A.H.A. de

Chapter 1

# General introduction

In neonatal care, treatment decisions for infants born at the limit of viability are often very complex. It is essential to involve parents in these decisions, taking into account their preferences, values, and concerns. The first part of this thesis explores the values that influence treatment decisions at the limit of viability. Additionally, as neonatal care continues to evolve with technological advancements such as artificial amnion and placenta technology (*"the artificial placenta"*), involving perspectives and values of key stakeholders becomes increasingly important. In the second part of this thesis, the perspectives of key stakeholders on the potential development of artificial placenta technology as a future treatment option for extreme prematurity are examined.

## Extreme premature birth

According to the World Health Organization (WHO), premature birth is defined as childbirth occurring before 37 weeks of gestation.[1] This affects millions of infants each year and is further categorized based on gestational age: extremely premature (<28 weeks), very premature (28-<32 weeks), and moderate to late premature (32-<37 weeks) as displayed in *figure 1*.[1] In 2020 alone, approximately 13.4 million babies were born prematurely worldwide, underscoring the need for effective interventions, enhanced healthcare systems, and informed decision-making by parents for this vulnerable group of infants.[2] Among all premature infants, those born extremely prematurely face the most significant challenges in neonatal care, high mortality rates, and often severe long-term consequences.[3]

Management in neonatal intensive care units (NICUs) includes interventions such as incubators, advanced respiratory support, infection prevention, and diagnostic examinations to monitor and address complications arising from the underdevelopment of vital organs, including the lungs, heart, and brain.[4] During their NICU stay, these infants are particularly vulnerable to life-threatening conditions such as respiratory distress syndrome, sepsis, intraventricular hemorrhage, necrotizing enterocolitis, and feeding difficulties, all of which stem from their extreme immaturity.[4]

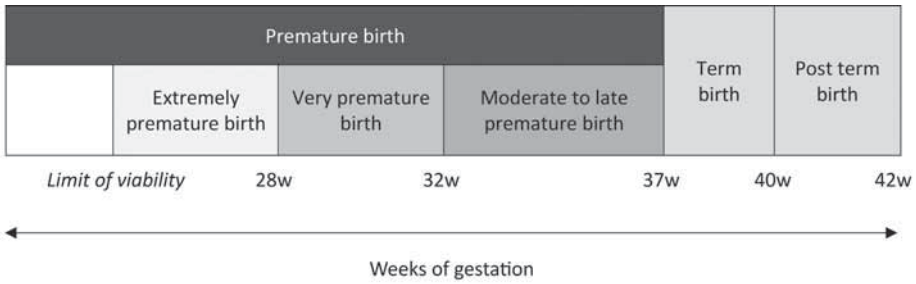


**Figure 1** Overview of definitions for premature birth according to the World Health Organization

Although NICU-care is continuously developing and improving, extremely premature infants frequently face long-term consequences.[3,5] These consequences can involve neurodevelopmental impairments such as cerebral palsy, intellectual disabilities, behavioral disorders, and sensory deficits like vision and hearing problems.[5] Additionally, they are

more prone to chronic health conditions such as bronchopulmonary dysplasia, asthma, and growth delays.[6,7] The impact of these challenges extends beyond the physical problems and consequences, often affecting the child's educational and social development.[5] As a result, many survivors require medical and psychological support when they get older.

## Viability

In the context of extreme premature birth, viability is an important but complex concept. It describes the ability of a premature infant to survive outside the womb. Viability is determined by biomedical and technological capacities, which allows for a distinction between natural viability and technical viability, as explained by De Proost and is schematically represented in *figure 2*.[8-10] Technical viability refers to the survival of a premature infant based on the availability of advanced medical technologies, and natural viability is the ability of an infant to survive without such interventions.[9] Technical viability is a "statistical property", as not every fetus will survive at the so-called limit of viability.[9] It depends on contextual variables, such as advances in perinatal medicine, insight into fetal development and innovations in pharmacological treatment. Globally, variations in resource availability, infrastructure, and expertise lead to differences in how viability is perceived. As a consequence, there is no universally accepted gestation age that defines viability.[8] Internationally, countries set their own thresholds for what is considered the limit of viability, often based on the gestational age at which survival is deemed possible with the available medical interventions together with societal values that are important.[8,11]

The concept of technical viability leads to what is often referred to as the "grey zone", a certain gestational range in which the outcomes of medical treatment for newborn infants are uncertain.[12] The definition of this zone varies between 22-26 weeks of gestation, with the specific upper and lower limits changing over time, across countries and different cultures.[12] These variations are influenced by medical advancements and resources, infrastructure, knowledge, sociocultural values, and ethical considerations.[13-15] Below the lower limit of the grey zone, neonatal care is considered medically futile or just not feasible.[13,16] For these infants, provision of care other than palliative comfort care is unreasonable.[13] Beyond the upper limit of the grey zone, the infant is mature enough to have a reasonable chance for a good outcome, therefore early intensive care treatment will be initiated.[13,16] In the grey zone, multiple options exist, ranging from early intensive care to palliative comfort care.[13]

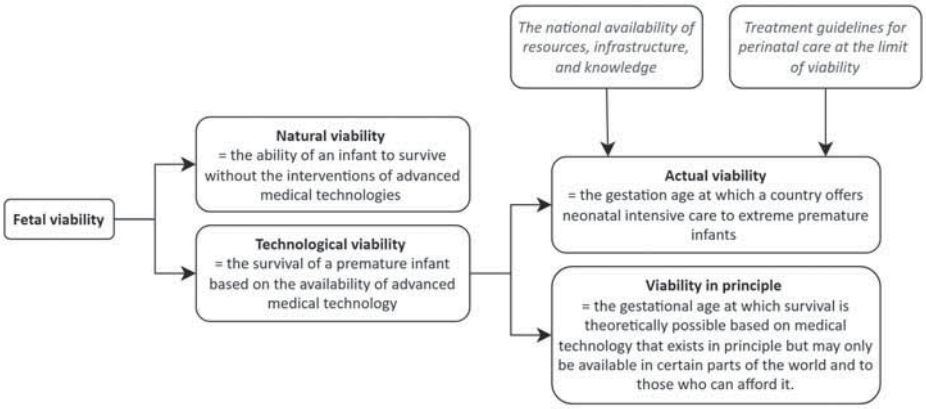


**Figure 2** Different interpretations of fetal viability based on the figure of De Proost et al, 2023, Viability, abortion and extreme prematurity: a critique

## Counselling and decision-making at the limit of viability

When an extremely premature birth at the limit of viability is imminent, parents are typically offered prenatal counseling.[17] There is no standardized universal approach to the structure or content of this counseling, but research highlights the importance of tailoring it to individual circumstances.[18-20] Generally, prenatal counseling provides parents with information about extreme prematurity, including survival rates, potential outcomes, and the expected postnatal care trajectory.[19-22] A primary objective of prenatal counseling in cases of extreme prematurity at the limit of viability is to support and guide parents in the decision-making process.[23,24]

After receiving counselling in the context of imminent extremely premature birth at the limit of viability, complex decisions must be made including the decision about treatment of the infant after birth. Depending on the guideline, it is often recommended to involve parents in discussions between early intensive care or palliative comfort care.[25] These conversations between parents and physicians are complex and emotionally overwhelming with a lot of information that needs to be processed.[26] In this state with a lot of uncertainty, parents have to navigate treatment decisions focusing on neonatal early intensive care or palliative comfort care at the limit of viability.[27,28] The decision to initiate early intensive care treatment comes with great prognostic uncertainty.[3] Initiating palliative comfort care means the infant will die. Since there is no 'best decision' in this situation, these kind of decisions are often characterized as "preference-sensitive" or "value-loaden"; thus, a shared decision-making approach becomes imperative.[29-31]

## Shared decision-making

Shared decision-making encompasses a systematic process in which healthcare professionals inform the patient – in this context the (future) parents - about the available treatment options, discuss the potential risks and benefits of each treatment option, and facilitate an

open dialogue about the preferences and values of the parents (*figure 3*).[30] This process includes a critical step known as value clarification, wherein healthcare providers assist parents in articulating their priorities and concerns, thus ensuring that the decisions made align closely with their wishes for their child's care.[30,32,33]

Despite the recognized importance of involving parents in these discussions, clinicians do not always engage them effectively in conversations about treatment options, particularly regarding resuscitation efforts following extremely preterm births.[32] Research indicates that barriers to effective shared decision-making often stem from a variety of factors, including time constraints, the emotional burden of the discussions, and differing perspectives on the best course of action.[34] Nonetheless, parents consistently express a strong desire for participation in these critical conversations, emphasizing the need for healthcare teams to navigate these dialogues with sensitivity and thoroughness.[35]



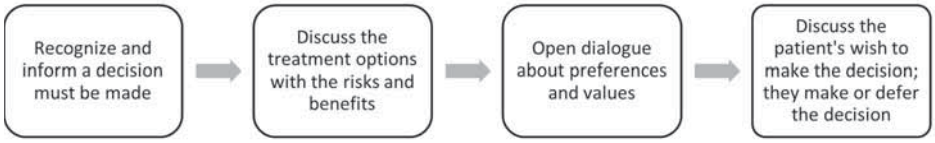


**Figure 3** Schematic representation of shared decision making based on the model by Stiggelbout et al.

## Value clarification

As described before, value clarification is a key component of shared decision-making. Value clarification focusses on helping patients identify and communicate their personal values, preferences, and priorities regarding treatment decisions. This process ensures that decisions align with what matters most to the patient. In the field of neonatology, it is known that understanding values is crucial, and should be a central part of the decision making process.[36-38] There are tools, such as decision aids, that help in the process of shared decision-making and presenting options and outcomes. However, these tools do not always directly show how to engage in value clarification or uncover what those values truly are.[33]

Box 1: Parents as surrogate decision makers
It is important to acknowledge the differences in decision-making between pediatric or neonatal medicine and adult medicine. While decision-making in adult medicine often draws on the patient's past behaviors or stated preferences to guide treatment choices, pediatric decisions lack such reference points.[39] Instead, parents must rely on their own values and goals when making healthcare decisions for their infant.[40] Deciding for yourself versus making a decision for someone else (so-called surrogate decision-making) influences treatment preferences.[41,42] In prenatal decision making, the parents are the surrogate decision makers for their unborn infant.

### *The dutch context regarding decision making at the limit of viability*

The prevalence of preterm births in the Netherlands was reported in 2021 at 6.6% (= approximately 1150 premature babies), with 0.15% (= 251 babies) being born between 24-26 weeks gestation.[43] Despite advancements in neonatal care, the survival rates for these

infants remain precarious; around 60% survive to discharge, but many of them are at risk of facing severe or moderate disabilities.[44]

At the start of this thesis, the guideline established in 2010 was in effect, defining the limit of viability as 24 weeks of gestation. Associated with this 2010 guideline, a counseling framework and an accompanying decision aid (www.keuzehulpvroeggeboorte.nl) were developed, based on findings from the Dutch PreCo studies.[45,46] One of the recommendations emphasized that shared decision-making was important, but should be personalized. The exploration of values was found to be really important, however not easy to do.[23] With this thesis, we hope to contribute to improving shared decision-making, especially value clarification at the limit of viability to help parents make value congruent decisions.

The most recent guideline in the Netherlands stems from 2024.[47] This revised guideline maintains the threshold for providing early intensive care at an estimated gestational age of 24+0 weeks. It states that individual factors influencing the survival chances and outcomes for the child must be taken into account. However, the professional associations (pediatrics and obstetrics) have stated that providing care before the estimated gestational age of 24 weeks is not yet feasible due to limitations in the capacity of highly specialized nurses, the availability of beds (in NICUs, obstetric high-care units, and peripheral pediatric wards), the organizational and financial impact on long-term follow-up care, and the potential legal implications related to the Termination of Pregnancy Act.[47] The upper limit for intensive care in the Netherlands is still set at 26+0 weeks of gestation. This creates a decision-making "*grey zone*" between ~24 and ~26 weeks, when parents should be involved in determining whether to pursue early intensive care or opt for palliative comfort care, as illustrated in *Figure 4*.[47] This grey zone in the Netherlands reflects the cultural and societal values that shape Dutch medical guidelines and policies.[11,48] Dutch society places significant emphasis on values such as personal freedom, the desire to minimize suffering, and the prioritization of quality of life. These values are deeply ingrained and are reflected in the country's laws, regulations, and medical guidelines.[11]

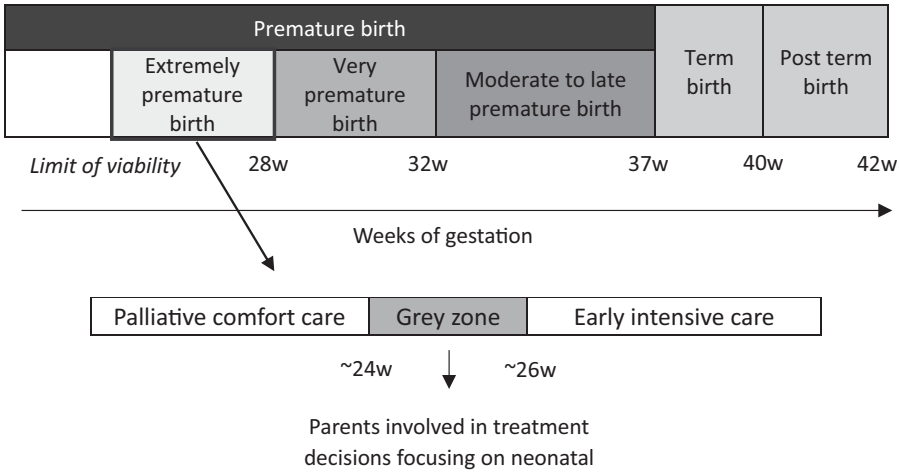


**Figure 4** Schematic representation of the Dutch situation

International grey zones differ from the Dutch grey zone, as each region defines its own boundaries. These limits are shaped by factors such as cultural norms, national policies, and healthcare practices, highlighting the inherent variability and complexity of decision-making in neonatal care.[11,49] Nevertheless, while the application of the grey zone may vary across cultures and countries, the issues and research presented in this thesis are universal and hold relevance for neonatal care worldwide.

## Innovations to improve neonatal care: artificial amnion and placenta technology

Advancements in neonatal care continue to shape neonatal care, influencing the possibilities at the limit of viability and the concept of viability itself. Important milestones in history are the development of the incubator, attention for nutrition and hygiene, and the pharmacological options like surfactant and antenatal steroids.[50]

One of the most recent developments in neonatal care is the development of artificial amnion and placenta technology. This technology aims to postpone the transition to extra uterine physiology by mimicking the liquid-based environment and function of the amniotic sac, amniotic fluid and placenta.51-55 The aim of this technology is to improve clinical outcomes by limiting complications, increasing survival rate and improving quality of life of the extreme prematures.54,55 Several research teams around the world are currently in the animal testing phase of developing this technology, with promising results (figure 5).51,54,56,57 The team at Children's Hospital of Philadelphia appears to be the furthest along in developing this technology, being in the process of proceeding to first-in-human trials in the coming years.[58]

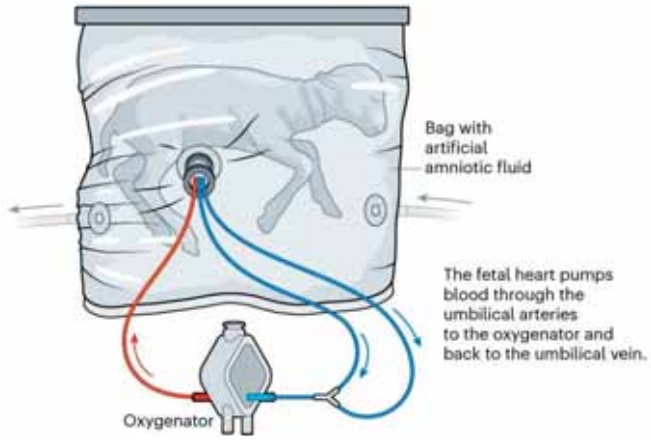


**Figure 5** Schematic representation of the animal model of artificial amnion and placenta technology. Image adapted from Max Koslov, Nature Publishing Group.

The development of this emerging technology and the upcoming first in-human trails raises many ethical, legal and practical questions.[59,60] It could have the potential to influence the 'grey zone' and/or the interpretation of the concept of viability in the future.[61] The ethical debate surrounding artificial amnion and placenta technology is complex, involving a diverse range of stakeholders—such as parents, developers, clinicians, and ethicists—each with distinct perspectives, concerns, and interests.[62] Part of responsibly designing a new technology is engaging all different stakeholders from basic research to implementation.[62] Stakeholders can provide valuable insights, arguments to support their views, conditions under which they deem the technology acceptable, and the values they wish to protect or want the technology to add. By reflecting on the ethical implications of artificial amnion and placenta technology, ethical considerations can be integrated into the technology's advancement.

Despite the importance of involving a broad spectrum of stakeholders, some perspectives seem to remain absent from current discussions. The perspectives of those not yet engaged—such as parents who have directly faced imminent or actual extreme prematurity and healthcare professionals actively working in perinatal care—represent a significant gap in the ethical discourse surrounding artificial amnion and placenta technology. These groups can provide firsthand insights into the lived realities of extreme prematurity and the practical challenges and opportunities associated with implementing such groundbreaking technology. To fill this gap, the second part of this thesis will explore the perspectives of Dutch parents who experienced an imminent or actual extremely premature birth and of Dutch healthcare professionals working in perinatal care.

### *The Dutch context of artificial amnion and placenta technology*

In the Netherlands, a consortium based at the TU Eindhoven is working on a Perinatal Life Support (PLS) system.[53,63] Within this PLS-system, the baby would receive oxygen and nutrients through the umbilical cord and an artificial placenta, allowing the organs to mature and develop more naturally. The PLS project also aims to overcome the significant challenge of pre-clinical safety testing by utilizing innovative simulation technology. This involves using a manikin, equipped with advanced monitoring and computational modeling, to simulate the birth of extremely premature infants. This technology provides valuable insights into fetal status and potential treatments, helping to refine the system before clinical trials.[64,65]



Internationally, several research groups are working on developing techniques to mimic the conditions of the uterus and placenta with the aim to improve outcomes and survival of extremely premature infants. While the Dutch consortium focusses on simulation technology for translation to human trials, these international research groups conduct research on the development of the technology, using animal models. To the best of our knowledge, there are currently five groups outside the Netherlands developing and testing their models in animals. The group in Michigan (USA) is working on the VV Preemie ECLS, while the groups in Perth (Australia) and Sendai (Japan) are focusing on their own model called the Ex-Vivo Uterine Environment (EVE). The team in Philadelphia (USA) is developing what is perhaps the most well-known model, the EXTra-uterine Environment for Neonatal Development (EXTEND). Additionally, groups in Barcelona (Spain) and Toronto (Canada) are also creating their own models.[66]

So, local Dutch advancements in artificial amnion and placenta technology contribute to the global research efforts in this field. While some themes and issues addressed in this thesis are influenced by cultural contexts, many of these challenges and insights are relevant worldwide, reflecting the universal nature of neonatal care and research. Through the results of our research, we aim to support the development of artificial amnion and placenta technology in an ethically responsible manner.

## Outline thesis

This thesis is part of the TINY-study (Toward INdividualized care for the Youngest), a Dutch research initiative involving three perinatal centers in The Netherlands: Leiden University Medical Center, Radboudumc Amalia Children's Hospital, and Erasmus MC-Sophia Children's Hospital. The TINY-study explores stakeholder perspectives on periviability guidelines, personalization, parental values, and artificial amnion and placenta technology.[48,67-71]

The first part of this thesis focusses on the parental values in decision-making at the limit of viability. The second part of this thesis describes the perspectives of different stakehold-

ers on the development of artificial amnion and placenta technology as potential future treatment for extreme prematurity.

### *Part one: Values in decision-making at the limit of viability*

Chapter 1 presents the results of a scoping review on parental perspectives in prenatal decision-making at the threshold of viability. We explore various studies on parental perspectives that are deemed important in decisions at the limit of viability. In the process of discussing our extracted data and writing the manuscript, Hiske and Dirk Jan - parents of an extremely premature infant born at a gestation of 24 weeks - collaborated with us and are included as co-author. Intermezzo 1 offers a personal account by Hiske and Dirk Jan, detailing their experience with premature birth and their decision-making process.

Chapter 2 describes the TINY-1 study, a qualitative focus group study with adults born extremely premature regarding their perspectives on what should be considered during the decision at the limit of viability. This study uniquely incorporates the voices of individuals living with the consequences of such decisions. Intermezzo 2 features a spin-off article written by TINY-1 participants, published in the Dutch medical journal *Medisch Contact.*

Chapter 3 describes the TINY-2 study, which uses individual interviews with parents of infants born between 23+0 to 26+0 weeks' gestation. It explores their considerations when deciding between intensive care and palliative comfort in the "grey zone."

### *Part two: Perspectives on the development of artificial amnion and placenta technology as potential future treatment for extreme prematurity.*

Chapter 4 provides a systematic review of ethics literature on artificial amnion and placenta technology, focusing on its intended use in extreme prematurity.

Chapter 5 presents our open peer commentary on a review providing an overview of the current ethical literature on the artificial placenta. In this commentary, we propose a different approach on how we believe the ethical debate on the artificial placenta can be enriched.

The TINY-3 study aimed to address a gap in the current literature by exploring the perspectives of various stakeholders on the development of artificial amnion and placenta technology, an essential step in the responsible design of new medical innovations. To initiate this study, we conducted a stakeholders meeting using a guidance ethics approach. Intermezzo 3 provides a summary of the report from this meeting, detailing the different phases of the guidance ethics methodology. The outcomes of this meeting formed the foundation for the subsequent TINY-3 studies, which consist of qualitative research designed to capture the perspectives of parents who experienced imminent or actual extreme premature birth, as well as healthcare professionals in perinatal care.

Chapter 6 describes the TINY-3a study, which explores the perspectives of experienced parents and healthcare professionals on designing responsible first-in-human trials of artificial amnion and placenta technology.

Chapter 7 describes the TINY-3b study, examining considerations for counseling and informed consent procedures in potential future trials of artificial amnion and placenta technology.

Chapter 8 described the TINY-3c study, exploring ethical concerns and considerations for the eventual clinical translation and implementation of artificial amnion and placenta technology.



### *Closing pages and recommendations*

This thesis ends with a general discussion that summarizes and analyzes the main findings. It also provides recommendation for clinical practice and future perspectives.

## Definitions and used terms explained

*Inspired by the table published in the thesis of Geurtzen.*[46]

| Used in the introduction and discussion of this thesis | Description | Alternatives |
|---|---|---|
| Limit of viability, Grey zone | The stage of fetal maturity that ensures a reasonable chance of extra-uterine survival. With active intervention, most infants born at 26 weeks and above have a high likelihood of survival, and virtually none below 22 weeks will survive. The chance of survival thus increases dramatically over these few weeks, and this crucial time window may be considered the period of periviability. | Limits of viability<br>Periviability<br>Threshold of viability<br>Extreme prematurity<br>Border of viability |
| Early intensive care | The resuscitation of an infant following extreme premature birth (including airway, breathing and circulation management) and the initiation of neonatal intensive care | Intensive care treatment<br>Resuscitation<br>(Active) care<br>(Active) support<br>(Active) treatment<br>(Active) intervention |
| Palliative comfort care | The withholding of early intensive care allowing parents to hold their baby following birth. Comfort of the baby will be assured and the newborn will die | Palliative care<br>Comfort care<br>No treatment<br>Withholding resuscitation |
| Value | An umbrella term referring to what matters to an individual, what they hold in high regard or an ideal, in this context relevant to a health decision. | Views<br>Beliefs<br>Perceptions<br>Perspectives<br>Considerations |
| Value clarification | The process of exploring what matters to an individual relevant to a given health decision. This definition emphasizes that what matters to an individual might be broader than attribute-specific values, but could also include other preferences. | Value elicitation<br>Formulation of values<br>Exploration of values |
| Artificial Amnion and Placenta Technology | Technology that mimics the function of amniotic fluid, the amniotic sac and the placenta, developed as treatment for extreme prematurity aiming to improve neonatal mortality and morbidity. | Artificial Placenta<br>Artificial Womb<br>Partial ectogenesis<br>Perinatal Life Support (PLS)<br>EXTEND |

## References


1. World Health Organization. Preterm birth factsheet 2023 [Available from: https://www.who.int/news-room/fact-sheets/detail/preterm-birth.
2. Ohuma EO, Moller AB, Bradley E, Chakwera S, Hussain-Alkhateeb L, Lewin A, et al. National, regional, and global estimates of preterm birth in 2020, with trends from 2010: a systematic analysis. Lancet. 2023;402(10409):1261-71.
3. Myrhaug HT, Brurberg KG, Hov L, Markestad T. Survival and Impairment of Extremely Premature Infants: A Meta-analysis. Pediatrics. 2019;143(2).
4. Morgan AS, Mendonça M, Thiele N, David AL. Management and outcomes of extreme preterm birth. BMJ. 2022;376:e055924.
5. Glass HC, Costarino AT, Stayer SA, Brett CM, Cladis F, Davis PJ. Outcomes for Extremely Premature Infants. Anesthesia & Analgesia. 2015;120(6).
6. Northway Jr WH, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. The New England journal of medicine. 1967;276(7):357-68.
7. Pierrat V, Marchand-Martin L, Guemas I, Matis J, Burguet A, Picaud JC, et al. Height at 2 and 5 years of age in children born very preterm: the EPIPAGE study. Arch Dis Child Fetal Neonatal Ed. 2011;96(5):F348-54.
8. Breborowicz GH. Limits of fetal viability and its enhancement. Early Pregnancy (Cherry Hill). 2001;5(1):49-50.
9. De Proost L, Verweij EJ, Geurtzen R, Zuijdwegt G, Verhagen E, Ismaili M'hamdi H. Viability, abortion and extreme prematurity: a critique. Clinical Ethics. 2023;18(4):385-92.
10. De Proost L. Navigating Periviability: On the ethics of personalization at the limit of viability [Dissertation]. Rotterdam, the Netherlands: Erasmus University; 2024.
11. De Proost L, Verweij EJT, Ismaili M'hamdi H, Reiss IKM, Steegers EAP, Geurtzen R, et al. The Edge of Perinatal Viability: Understanding the Dutch Position. Front Pediatr. 2021;9:634290.
12. Seri I, Evans J. Limits of viability: definition of the gray zone. J Perinatol. 2008;28 Suppl 1:S4-8.
13. Gillam L, Wilkinson D, Xafis V, Isaacs D. Decision-making at the borderline of viability: Who should decide and on what basis? J Paediatr Child Health. 2017;53(2):105-11.
14. Mactier H, Bates SE, Johnston T, Lee-Davey C, Marlow N, Mulley K, et al. Perinatal management of extreme preterm birth before 27 weeks of gestation: a framework for practice. Arch Dis Child Fetal Neonatal Ed. 2020;105(3):232-9.
15. Wilkinson D, Verhagen E, Johansson S. Thresholds for Resuscitation of Extremely Preterm Infants in the UK, Sweden, and Netherlands. Pediatrics. 2018;142(Suppl 1):S574-s84.
16. Wilkinson DJ. Gestational ageism. Arch Pediatr Adolesc Med. 2012;166(6):567-72.
17. De Proost L, Geurtzen R, Ismaili M'hamdi H, Reiss I, Steegers E, Joanne Verweij EJ. Prenatal counseling for extreme prematurity at the limit of viability: A scoping review. Patient Educ Couns. 2022;105(7):1743-60.
18. Mehrotra A, Lagatta J, Simpson P, Kim UO, Nugent M, Basir MA. Variations among US hospitals in counseling practices regarding prematurely born infants. J Perinatol. 2013;33(7):509-13.
19. Duffy D, Reynolds P. Babies born at the threshold of viability: attitudes of paediatric consultants and trainees in South East England. Acta Paediatr. 2011;100(1):42-6.
20. Geurtzen R, van Heijst AF, Babarao S, Molloy E, Draaisma JM, Hogeveen M. Practices in antenatal counseling for extremely premature infants amongst European trainees. J Matern Fetal Neonatal Med. 2016;29(24):3956-9.
21. Geurtzen R, Van Heijst A, Hermens R, Scheepers H, Woiski M, Draaisma J, et al. Preferred prenatal counselling at the limits of viability: a survey among Dutch perinatal professionals. BMC Pregnancy Childbirth. 2018;18(1):7.
22. Boland RA, Davis PG, Dawson JA, Doyle LW. What are we telling the parents of extremely preterm babies? Aust N Z J Obstet Gynaecol. 2016;56(3):274-81.

23. Geurtzen R, van Heijst A, Draaisma J, Ouwerkerk L, Scheepers H, Woiski M, et al. Professionals' preferences in prenatal counseling at the limits of viability: a nationwide qualitative Dutch study. Eur J Pediatr. 2017;176(8):1107-19.
24. Watson K, Stokes TA. Neonatology consultations for preterm labour beyond the grey zone: reconceptualising our goals. Acta Paediatr. 2015;104(5):442-3.
25. Payot A, Gendron S, Lefebvre F, Doucet H. Deciding to resuscitate extremely premature babies: how do parents and neonatologists engage in the decision? Soc Sci Med. 2007;64(7):1487-500.
26. Gallagher K, Shaw C, Parisaei M, Marlow N, Aladangady N. Attitudes About Extremely Preterm Birth Among Obstetric and Neonatal Health Care Professionals in England: A Qualitative Study. JAMA Netw Open. 2022;5(11):e2241802.
27. Akkermans AA, Lamerichs J, Schultz MJM, Cherpanath T, van Woensel J, van Heerde MM, et al. How doctors actually (do not) involve families in decisions to continue or discontinue life-sustaining treatment in neonatal, pediatric, and adult intensive care: A qualitative study. Palliat Med. 2021;35(10):1865-77.
28. Beyer MF, Kuehlmeyer K, Mang P, Flemmer AW, Führer M, Marckmann G, et al. "We Absolutely Had the Impression That It Was Our Decision"-A Qualitative Study with Parents of Critically Ill Infants Who Participated in End-of-Life Decision Making. Children (Basel). 2022;10(1).
29. Lantos JD. Ethical Problems in Decision Making in the Neonatal ICU. N Engl J Med. 2018;379(19):1851-60.
30. Stiggelbout AM, Pieterse AH, De Haes JC. Shared decision making: Concepts, evidence, and practice. Patient Educ Couns. 2015;98(10):1172-9.
31. Kaempf JW, Kockler N, Tomlinson MW. Shared decision-making, value pluralism and the zone of parental discretion. Acta Paediatr. 2018;107(2):206-8.
32. Tucker Edmonds B, Hoffman SM, Laitano T, Bhamidipalli SS, Jeffries E, Fadel W, et al. Values clarification: Eliciting the values that inform and influence parents' treatment decisions for periviable birth. Paediatr Perinat Epidemiol. 2020;34(5):556-64.
33. Witteman HO, Ndjaboue R, Vaisson G, Dansokho SC, Arnold B, Bridges JFP, et al. Clarifying Values: An Updated and Expanded Systematic Review and Meta-Analysis. Med Decis Making. 2021;41(7):801-20.
34. Parish O, Williams D, Odd D, Joseph-Williams N. Barriers and facilitators to shared decision-making in neonatal medicine: A systematic review and thematic synthesis of parental perceptions. Patient Educ Couns. 2022;105(5):1101-14.
35. Geurtzen R, Draaisma J, Hermens R, Scheepers H, Woiski M, van Heijst A, et al. Various experiences and preferences of Dutch parents in prenatal counseling in extreme prematurity. Patient Educ Couns. 2018;101(12):2179-85.
36. Geurtzen R, van Heijst A, Draaisma J, Ouwerkerk L, Scheepers H, Hogeveen M, et al. Prenatal counseling in extreme prematurity - Insight into preferences from experienced parents. Patient Educ Couns. 2019;102(8):1541-9.
37. Boss RD, Hutton N, Sulpar LJ, West AM, Donohue PK. Values parents apply to decision-making regarding delivery room resuscitation for high-risk newborns. Pediatrics. 2008;122(3):583-9.
38. Kaempf JW, Tomlinson MW, Campbell B, Ferguson L, Stewart VT. Counseling pregnant women who may deliver extremely premature infants: medical care guidelines, family choices, and neonatal outcomes. Pediatrics. 2009;123(6):1509-15.
39. Zikmund-Fisher BJ, Sarr B, Fagerlin A, Ubel PA. A matter of perspective: choosing for others differs from choosing for yourself in making treatment decisions. J Gen Intern Med. 2006;21(6):618-22.
40. Lipstein EA, Brinkman WB, Britto MT. What is known about parents' treatment decisions? A narrative review of pediatric decision making. Med Decis Making. 2012;32(2):246-58.
41. Rhodes R, Holzman IR. The not unreasonable standard for assessment of surrogates and surrogate decisions. Theor Med Bioeth. 2004;25(4):367-85.
42. Tunney RJ, Ziegler FV. Toward a Psychology of Surrogate Decision Making. Perspect Psychol Sci. 2015;10(6):880-5.
43. 2022. Available from: geraadpleegd via: www.peristat.nl.

44. van Beek PE, Groenendaal F, Broeders L, Dijk PH, Dijkman KP, van den Dungen FAM, et al. Survival and causes of death in extremely preterm infants in the Netherlands. Arch Dis Child Fetal Neonatal Ed. 2021;106(3):251-7.
45. Geurtzen R, van Heijst AFJ, Draaisma JMT, Kuijpers L, Woiski M, Scheepers HCJ, et al. Development of Nationwide Recommendations to Support Prenatal Counseling in Extreme Prematurity. Pediatrics. 2019;143(6).
46. Geurtzen R. Prenatal counselling in extreme prematurity [Dissertation]. Nijmegen, the Netherlands: Radboud University; 2019.
47. Perinataal beleid bij Extreme vroeggeboorte (2024).
48. Verweij EJ, De Proost L, Hogeveen M, Reiss IKM, Verhagen AAE, Geurtzen R. Dutch guidelines on care for extremely premature infants: Navigating between personalisation and standardization. Semin Perinatol. 2022;46(2):151532.
49. Guillén Ú, Weiss EM, Munson D, Maton P, Jefferies A, Norman M, et al. Guidelines for the Management of Extremely Premature Deliveries: A Systematic Review. Pediatrics. 2015;136(2):343-50.
50. Philip AG. The evolution of neonatology. Pediatr Res. 2005;58(4):799-815.
51. Partridge EA, Davey MG, Hornick MA, McGovern PE, Mejaddam AY, Vrecenak JD, et al. An extra-uterine system to physiologically support the extreme premature lamb. Nat Commun. 2017;8:15112.
52. De Bie FR, Davey MG, Larson AC, Deprest J, Flake AW. Artificial placenta and womb technology: Past, current, and future challenges towards clinical translation. Prenat Diagn. 2021;41(1):145-58.
53. van der Hout-van der Jagt MB, Verweij EJT, Andriessen P, de Boode WP, Bos AF, Delbressine FLM, et al. Interprofessional Consensus Regarding Design Requirements for Liquid-Based Perinatal Life Support (PLS) Technology. Front Pediatr. 2021;9:793531.
54. Coughlin MA, Werner NL, Church JT, Perkins EM, Bryner BS, Barks JD, et al. An Artificial Placenta Protects Against Lung Injury and Promotes Continued Lung Development in Extremely Premature Lambs. Asaio j. 2019;65(7):690-7.
55. Yasufuku M, Hisano K, Sakata M, Okada M. Arterio-venous extracorporeal membrane oxygenation of fetal goat incubated in artificial amniotic fluid (artificial placenta): influence on lung growth and maturation. J Pediatr Surg. 1998;33(3):442-8.
56. Usuda H, Watanabe S, Miura Y, Saito M, Musk GC, Rittenschober-Böhm J, et al. Successful maintenance of key physiological parameters in preterm lambs treated with ex vivo uterine environment therapy for a period of 1 week. Am J Obstet Gynecol. 2017;217(4):457.e1-.e13.
57. Eixarch E, Illa M, Fucho R, Rezaei K, Hawkins-Villarreal A, Bobillo-Pérez S, et al. An Artificial Placenta Experimental System in Sheep: Critical Issues for Successful Transition and Survival up to One Week. Biomedicines. 2023;11(3).
58. Kozlov M. Human trials of artificial wombs could start soon. Here's what you need to know. Nature. 2023;621(7979):458-60.
59. Werner KM, Baker AC, Mercurio MR. Unique ethical considerations of the artificial womb and placenta: the threshold for patient eligibility in clinical trials. J Perinatol. 2023;43(11):1335-6.
60. Kukora SK, Mychaliska GB, Weiss EM. Ethical challenges in first-in-human trials of the artificial placenta and artificial womb: not all technologies are created equally, ethically. J Perinatol. 2023;43(11):1337-42.
61. Di Stefano L, Mills C, Watkins A, Wilkinson D. Ectogestation ethics: The implications of artificially extending gestation for viability, newborn resuscitation and abortion. Bioethics. 2020;34(4):371-84.
62. Verweij EJ, De Proost L, van Laar J, Frank L, Obermann-Borstn SA, Vermeulen MJ, et al. Ethical Development of Artificial Amniotic Sac and Placenta Technology: A Roadmap. Front Pediatr. 2021;9:793308.
63. Heyer J, Schubert F, Seitz AL, Steinle Y, Arens J, Orlikowsky T, et al. A Volume-Adjustable Artificial Womb for Extremely Preterm Infants. Transpl Int. 2024;37:12947.
64. van Haren JS, Delbressine FLM, Schoberer M, te Pas AB, van Laar JOEH, Oei SG, et al. Transferring an extremely premature infant to an extra-uterine life support system: a prospective view on the obstetric procedure. Frontiers in Pediatrics. 2024;12.

65. van Haren JS, van der Hout-van der Jagt MB, Meijer N, Monincx M, Delbressine FLM, Griffith XLG, et al. Simulation-based development: shaping clinical procedures for extra-uterine life support technology. Advances in Simulation. 2023;8(1):29.
66. De Bie FR, Binion CC, Antiel RM. Artificial womb technology – A more physiologic solution to treating extreme prematurity. European Journal of Obstetrics & Gynecology and Reproductive Biology: X. 2025;25:100359.
67. de Boer A, De Proost L, de Vries M, Hogeveen M, de Vries MC, Verweij E, et al. Voices of experience: what Dutch parents teach us about values and intuition in periviable decisions. Arch Dis Child Fetal Neonatal Ed. 2024.
68. de Boer A, De Proost L, de Vries M, Hogeveen M, Verweij E, Geurtzen R. Perspectives of extremely prematurely born adults on what to consider in prenatal decision-making: a qualitative focus group study. Arch Dis Child Fetal Neonatal Ed. 2023.
69. De Proost L, de Boer A, Reiss IKM, Steegers EAP, Verhagen AAE, Hogeveen M, et al. Adults born prematurely prefer a periviability guideline that considers multiple prognostic factors beyond gestational age. Acta Paediatr. 2023;112(9):1926-35.
70. De Proost L, de Boer A, Verhagen E, Hogeveen M, Geurtzen R, Verweij E. Voices of experience: insights from Dutch parents on periviability guidelines and personalisation. Arch Dis Child Fetal Neonatal Ed. 2024.
71. Geurtzen R, De Proost L, Verhagen AAE, Reiss IKM, Hogeveen M, Verweij EJT. Dutch professionals' discussion preferences with the parents of extremely premature infants varied, but the trend was towards shared decision-making. Acta Paediatr. 2023;112(6):1200-8.