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

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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]

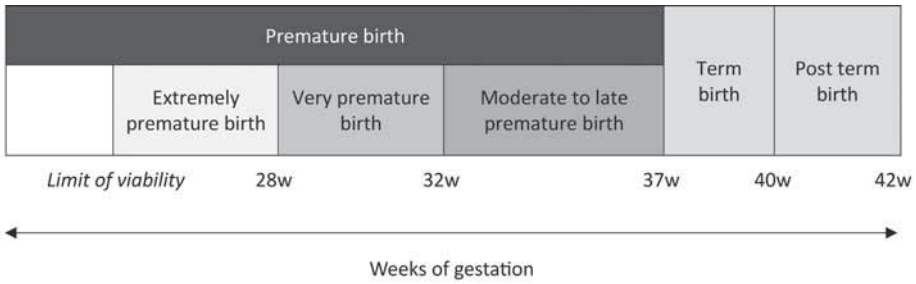

Figure 1 Overview of definitions for premature birth according to the World Health Organization

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]

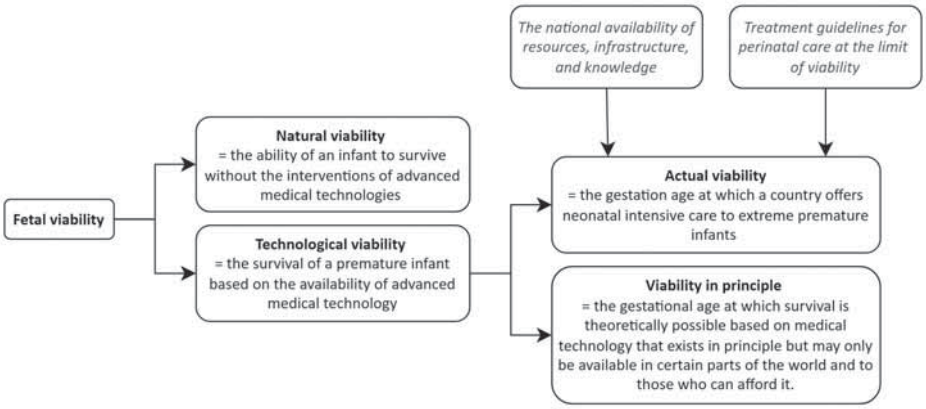

Figure 2 Different interpretations of fetal viability based on the figure of De Proost et al, 2023, Viability, abortion and extreme prematurity: a critique

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]

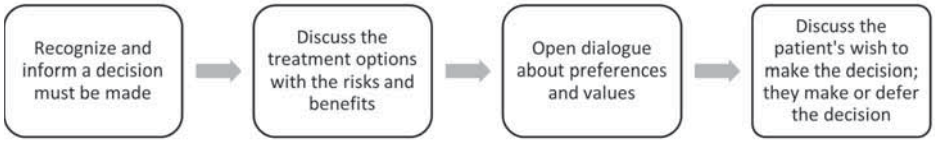

Figure 3 Schematic representation of shared decision making based on the model by Stiggelbout et al.

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]

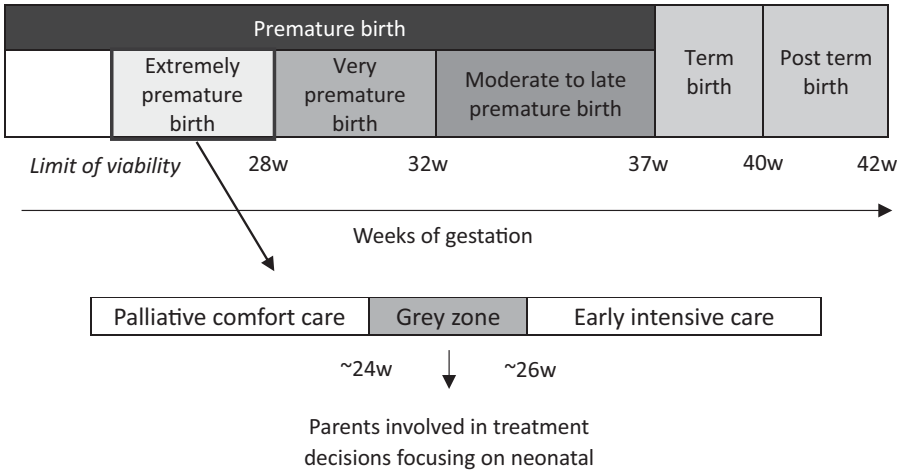

Figure 4 Schematic representation of the Dutch situation

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]

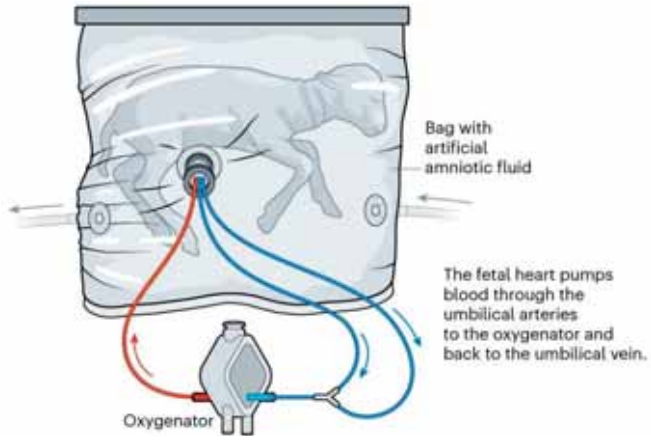

Figure 5 Schematic representation of the animal model of artificial amnion and placenta technology. Image adapted from Max Koslov, Nature Publishing Group.

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 Periviability Threshold of viability Extreme prematurity 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 Resuscitation (Active) care (Active) support (Active) treatment (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 Comfort care No treatment 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 Beliefs Perceptions Perspectives 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 Formulation of values 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 Artificial Womb Partial ectogenesis Perinatal Life Support (PLS) EXTEND

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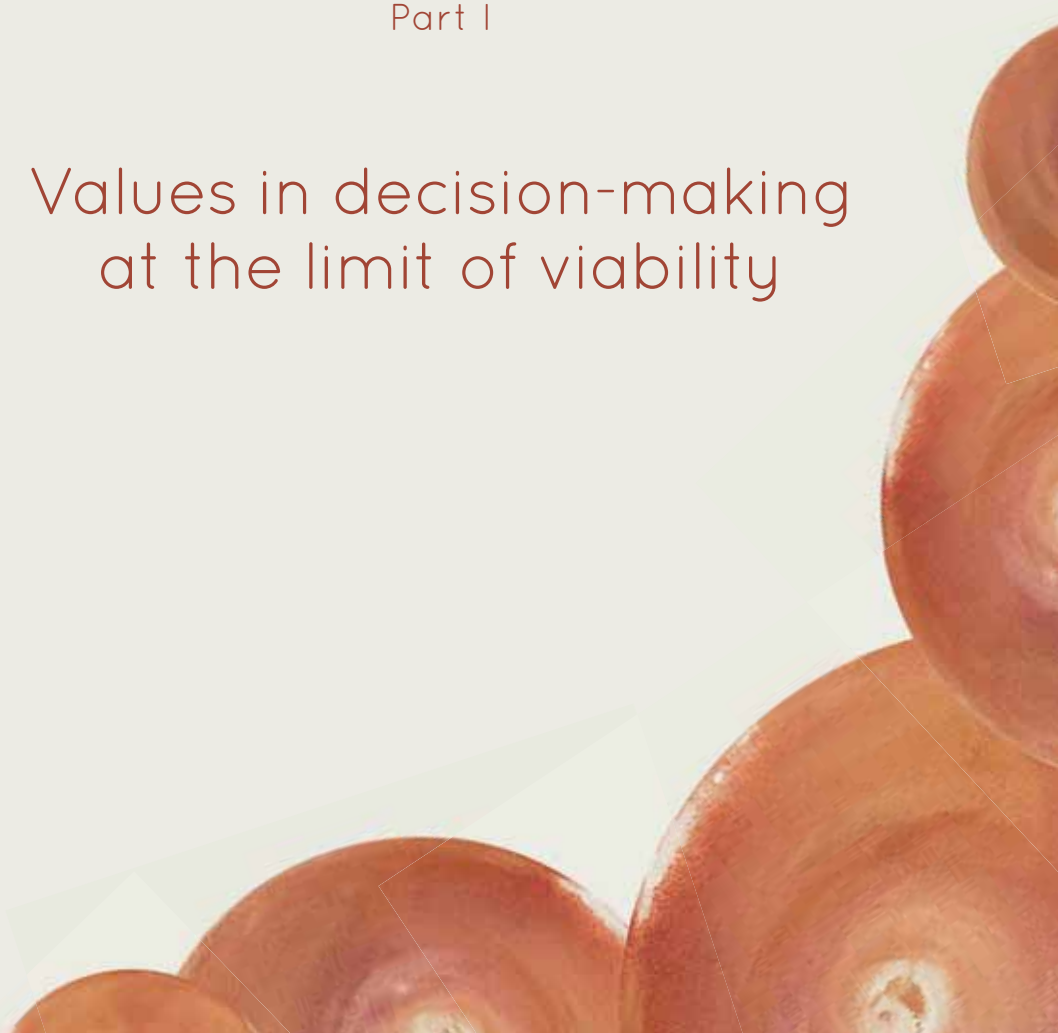
Part I

Values in decision-making at the limit of viability



Chapter 2

A scoping review of parental values during prenatal decisions about treatment options after extremely premature birth

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Acta Paediatrica, 2023

Abstract

Aim: To describe what is known in the literature about parental perspectives in making prenatal decisions about treatment after birth at the limit of viability, as a better understanding of parental values can help professionals support parents as they decide.

Methods: PubMed, Cochrane, Embase, CINAHL, PsycINFO and Web of Science were searched to identify relevant literature from 1 January 2010 to 22 April 2022 on parental decision making. Data were extracted from selected studies and organized into themes. The final themes were formed through collaboration with the parents of a premature infant born at 24 weeks.

Results: Of the 15,159 papers examined, 17 were included. Parental perspectives were described in terms of long-term outcomes for the infant, survival, protection against the burden of neonatal treatment, long-term impact on the family, religion and spiritual beliefs, to do everything possible, hope, sense of responsibility, wanting the best, doing what is right, giving a chance and the influence of experience.

Conclusion: The extracted parental perspectives show the complexity of these decisions. Some perspectives were clear, but others were multi-interpretable. Increasing the understanding of common parental perspectives can help improve shared prenatal decisions and lead to further improvement and personalisation of the process**.**

Background

Parents need to be involved in prenatal decisions about neonatal treatment if their baby is likely to be born extremely preterm -- in the grey zone, which is between 22 and 26 weeks of gestation, depending on time, country and culture.[1-3] The two treatment options in this grey zone are intensive care and comfort care. Intensive care treatment comes with great uncertainty regarding the outcome: some infants will not survive, some will go through life with one or more disabilities, and others will grow up without problems.[4]

As decisions in the grey zone are value laden,[5] a shared decision-making approach is recommended.[6-9] This involves mutual recognition of the need for a decision, followed by a discussion of the treatment options with their pros and cons, as well as an exploration of the parental values to be incorporated.[10,11] This exploration, known as *values clarification*, will allow treatment decisions to be aligned with personal goals and circumstances.[12] When a prenatal decision must be made, the preferences and values of the parents, who represent the unborn child, should be explored.[13]

Previous research has focused mainly on decision-making models and the preferred roles of parents and healthcare providers as they make decisions.[14] Although clarifying values is considered an essential aspect of shared decision making,[8,15,16] it is not always practised in prenatal decision making.[16] Improved understanding and identification of common parental values can help professionals support parents as they decide. The aim of this study, therefore, is to describe what has been published in the literature about the parental perspectives involved in prenatal decision making in cases of extreme prematurity.

Methods

This scoping review was guided by an article written by Micah Peters[17] and the checklist provided in the PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation; PRISMA stands for Preferred Reporting Items for Systematic reviews and Meta-Analyses.[18]

Search and study selection

In consultation with a literature specialist, we systematically searched PubMed, Cochrane, Embase, CINAHL, PsycINFO and Web of Science. The complete PubMed search is provided in *Appendix S1*. The databases were searched for literature published between 1 January 2010 and 22 April 2022. Reference lists of the included papers and related systematic reviews were screened to identify additional references. The results were collected in Endnote X9, a reference management tool (Clarivate, Philadelphia, USA) and deduplicated prior to screening. The deduplicated results were imported into an online reviewing system (Rayyan, Oxford, UK).[19]

Two authors (AB and RG) independently performed a title and abstract screening, followed by a full-text screening. The eligibility criteria are summarised in *Table 1*. Disagreements were settled through discussion with two authors (MV and MH).

Table 1: Eligibility criteria

Inclusion criteria	Exclusion criteria
The focus of the paper on prenatal decision-making regarding treatment after birth at the limit of viability; intensive care treatment or comfort care	Does not meet the inclusion criteria
The research population involves parents who experienced actual or imminent extremely premature birth at the limit of viability	Guidelines, expert opinions and reviews
Describing parental perspectives, arguments, considerations or specific values regarding the treatment options at the limit of viability	Publication that reported prompted perspectives, so they were not spontaneously named by the parents
English or Dutch	Unable to retrieve the abstract or the full-text paper
	Publications performed before 2010

Data analysis

Data pertaining to parental perspectives were charted from the included studies, using a data extraction tool made in Microsoft Excel (Microsoft 365 MSO, version 2202, UK).[17] We have used the term parental perspectives in this article to refer to several aligned items, such as parental perspectives, considerations, arguments, values and views. The key findings reported in *Table S2* are those of our research aim and are not necessarily similar to the key findings of the original manuscripts.

The authors developed a coding strategy prior to data extraction and adjusted it throughout the review process. To minimise extraction errors, two authors (AB and RG) independently extracted text parts from the included manuscripts. When papers did not exclusively focus on extreme prematurity or parents, the potentially eligible data were extracted except when they were explicitly described in another context. Thematic analysis was used to organise the extracted data into themes, which were substantiated with illustrative quotes from the included studies. Our research team (AB, RG, MV, MH and JV) collaborated with the parents (HD and DB) of a premature infant born at 24 weeks in 2020 to discuss and form the final themes derived from the data.

Results

Figure 1 presents the PRISMA flowchart of the inclusion process. The literature search revealed 15,159 deduplicated records, from which 17 papers were selected for inclusion in this review. Most of the studies were conducted in the United States (n=12)[20-31] and the others came from Canada (n=2),[32,33] Switzerland (n=1),[34] Norway (n=1)[35] and the Netherlands (n=1).[14] An overview of the characteristics of all included studies can be found in *Table*

S2. The results are charted in order of frequency, starting with the theme that was covered in the most papers. *Figure 2* provides a graphical display of the results.

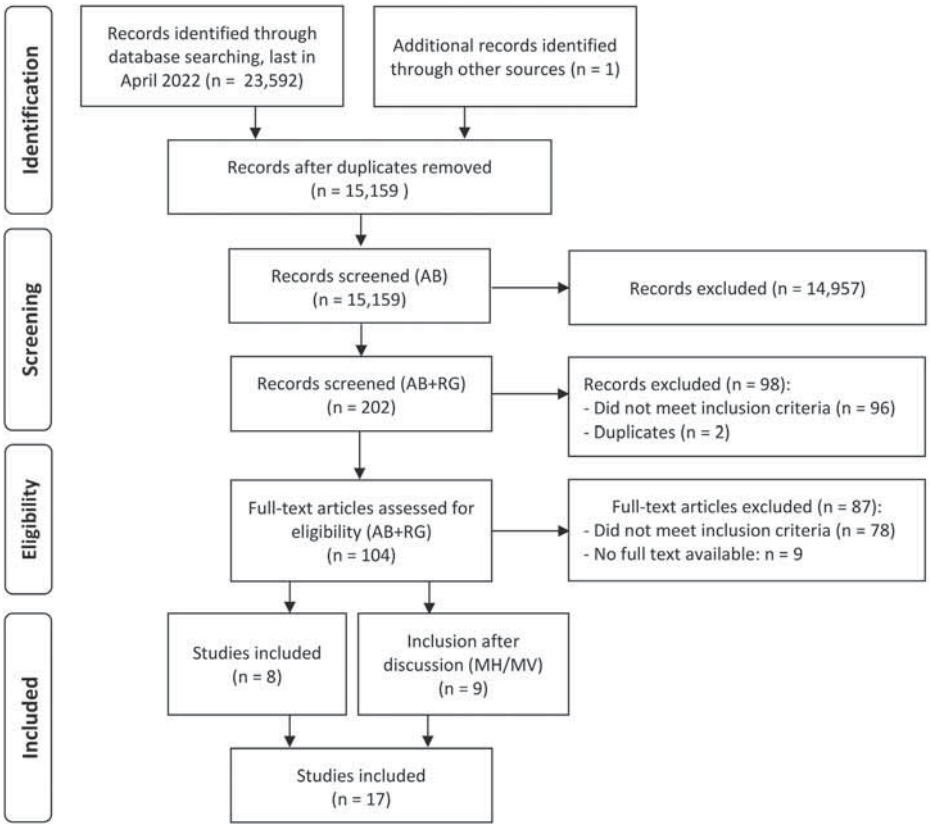

Figure 1 Prisma flowchart of results

Long-term outcomes for the infant

Many parents featured in the papers were concerned about the potential long-term outcomes for their premature infant, in terms of disabilities,[14,20,22,24,28,29,33,35] neurological or non-neurological complications[14,25,29,30,32,33] and quality of life.[14,27,29,30] These concerns were often cited as factors in parental decision-making about neonatal treatment, with some parents opting for comfort care. However, many parents chose intensive care despite these concerns, as they prioritised the infant's life. Opinions about acceptable long-term outcomes and the perception of the presumed quality of life of a disabled child were personal and differed amongst parents, as did the extent to which those outcomes played a role in the decision. As one parent stated: "*If I deliver this early, knowing that baby could have -- you know -- disabilities is the reason why I said do not resuscitate*".[24] Other parents said they may not have chosen resuscitation if they had known the potential complications[32] or to protect their child from becoming a vegetable.[30]

Other long-term considerations and preferred outcomes were described as a dignified existence[14] or a healthy infant[24], leading either to a decision for comfort care or an unspecified decision. Independence, participation in society and prognosis of intact survival were also reported as important considerations.[14]

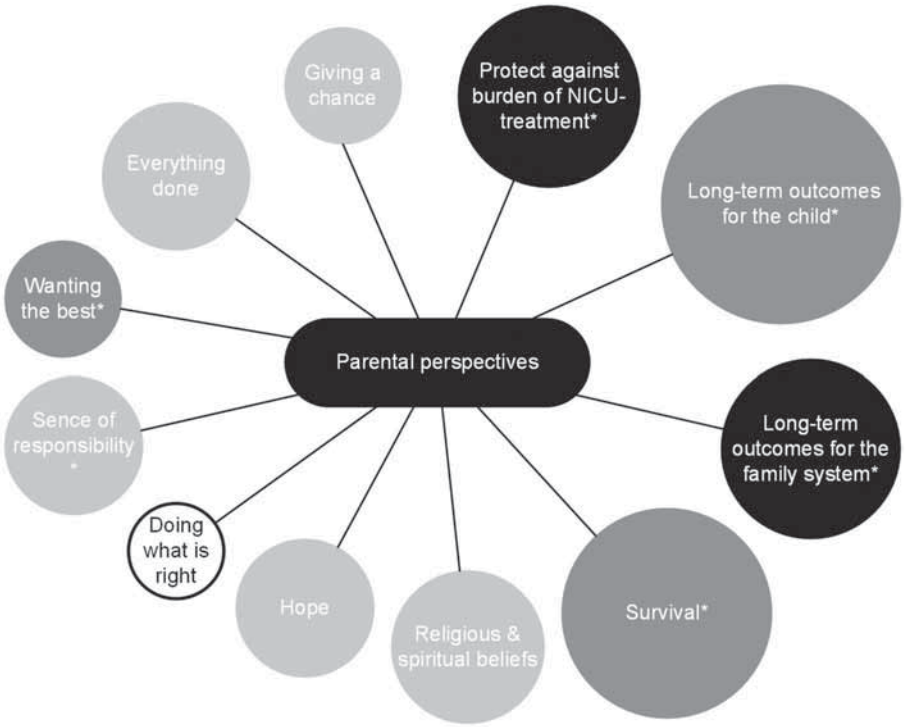

Figure 2 Graphical display of the parental perspectives extracted from the included literature. Each perspective is circled, with the circle radius proportional to the number of papers in which it is mentioned. The colour of the circle is based upon the choice (if this was recorded) made by the parents who expressed this perspective. Black = comfort care, light grey = intensive care treatment, dark grey = both comfort care and intensive care treatment. A white circle or a * in the circle means that in some papers in which parents expressed this perspective, no mention was made of the parental choice.

Parental concerns regarding the infant's future quality of life were also raised. One parent said, "*So, I think the majority of that decision would be based on the quality of life that your child would have".*[30] These concerns led to decisions for comfort care or for decisions that remained unspecified.

Survival

This theme covered different aspects of survival, including its general potential and specific probability. Some parents viewed the potential for survival as a reason to initiate intensive care treatment, while others, having weighed the probability of survival against the risk of short-term suffering or complications, opted for comfort care. When parents believed there

was a reasonable chance of long-term survival, they were likelier to choose intensive care. However, some parents were not concerned about potential complications and morbidities as long as their child survived.[14,20,26,29-31] Others were more focused on avoiding unnecessary suffering for their infant if the chances of survival were low[27,33]; as one parent argued: "*We don't want to have to put a child through something that she's not going to survive anyway*".[27]

Protection against the burden of treatment

When faced with the decision, parents were concerned about the pain and suffering that intensive care treatment could cause.[14,24,27,29-32,34] They weighed up the disadvantages of potential suffering against the benefits of comfort care.[27] One mother argued that the benefit of not resuscitating was "*that the baby would not be in pain and would probably pass quickly and not with stress*".[27] It was reported that parents would not have initiated intensive care treatment had they known how much their child would have to suffer in the neonatal intensive care unit (NICU).[32] However, although most parents considered short-term suffering to be an important argument in favour of comfort care, some still chose intensive care treatment in spite of their concerns about it.

Long-term impact on the family

Some parents reported concerns about long-term outcomes for themselves and the impact on other family members when choosing intensive care treatment.[14,26,28,29,32,35] One study reported parents as saying that family life, which also matters, could be very different with a premature child.[35] In two papers based on data gathered in the USA, mothers expressed their fear of the financial consequences.[23,25]

Religion and spiritual beliefs

Several papers discussed parents' reliance on spirituality, faith and religion to make the decision to initiate intensive care treatment.[20,21,24,27,29,30,33] Parents believed the decision should be left to "*God*".[20,21] Faith helped them to maintain hope[20] and not give up, despite the risks.[27] One mother argued: "*She's gonna be fine ... I keep referring back to God has the last say, so ... He's not gonna give me or my partner too much that we can't bear*".[30]

Everything done

In some of the papers, parents justified their decision for intensive care treatment by saying they wanted everything done.[14,26,30,31,34,35] As one parent explained, "*We had the option not to do anything and then she would die after a while. Or we had the option to try everything possible ... We discussed this and we said we would try everything*".[34] The authors of one study worried that failure to define the concept of everything done could cause a misperception of the delivered care. One of the parents in that study felt that her infant did not receive appropriate care in spite of her insistence that everything should be done.[31]

Hope

Hope appeared to be important in prenatal counselling, especially for parents who chose intensive care.[20,27,29,31,35] Despite the physicians' medical information about risks of disability or death, parents based their decision on their hopes that their infant would survive, would be fine or would be better than expected.[31] One article reported that some parents wanted hope while others wanted realism.[29] Hope could be helpful for parents. As one stated: "*The pain is going to be there no matter what, so I didn't mind trying to have hope".*[29] This theme had some overlap with the Survival subtheme described above.

Sense of responsibility

Papers addressing this theme reported that parents chose either intensive care treatment or made no clear decision. Several papers described how parents felt they had to advocate for their infant and take responsibility.[14,24,25,35] Parents felt responsible for making the final decision[14,30,35] or were convinced that it was their job to take responsibility for and protect their infant.[14] They needed to be assured that there was no right or wrong in making their decision.[14] Another article described how parents experienced an instinct to save the infant; as one explained: "*You experience that the survival instinct when you are pregnant, and the protection instinct after birth, is so strong that it is difficult in the situation … I do not know how long it took me to arrive at a more nuanced view".*[35]

Giving a chance

Parents choosing intensive care treatment described giving the infant a fighting chance as important.[14,24,27,30] One mother justified her decision by saying: "*Give her an opportunity, give her a chance, don't write her off".*[27] Choosing comfort care felt like denying the infant the chance to fight,[14] and parents just wanted to give their infant a chance to live because they felt the infant deserved it as much as any other baby.[27]

Wanting the best for the infant

In some of the studies, parents argued that they wanted the best for their infant[24,26,35] and act in the child's best interest[35]: "*The whole thought process the whole time was … just whatever is going to be the best outcome for her".*[26] However, parents differed in their interpretations of the best; for some, it meant choosing intensive care treatment, for others, comfort care.

Doing what is right

While making their decision, parents wanted to do what was most '*natural and right'*, without specifying to what natural and right pertained or to which decision this led.[20,22] Another article reported parents as saying they anticipated their possible regret.[29]

Influence of experience

Parents' decisions could be influenced by prior experiences, either their own[20,24] or an acquaintance's,[21,24,29] with a premature or extremely premature infant treated in the NICU.

Discussion

We carried out a scoping review of parental perspectives on decision making at the limits of viability. Our results offer insight into the most common values underlying parental decisions. Complex and multi-layered, some themes reflect the weighing of factual information about outcomes for infants and families, as well as numerous underlying and potentially conflicting values. Other themes reflect a process preference, such as the desire to do everything possible, or reflect feelings or intuitions, such as the instinct to save the child. The results demonstrate parents' difficulties in clarifying and verbalising their values in a sudden situation that provokes anxiety and is laden with values. Similarly, physicians may not be fully equipped to clarify parental values and fail to recognise that parental perspectives can be unclear and open to interpretation or misinterpretation.[15,36-38] This can make it challenging to provide guidance and support to parents. One perspective can be interpreted differently by different parents and lead to different decisions, so that some will decide to initiate intensive care treatment and others comfort care, based on the same perspective. For example, some parents could believe that everything done means everything technically possible, while others think the phrase means that they simply want to feel that they have done all they could for their child.[39]

The results of this review raise questions about the extent to which feelings and intuitions, rather than explicit deliberations about values, guide the choice of intensive care treatment or comfort care. Themes, such as everything done or hope, suggest that feelings or intuitions may be more important than explicit deliberations about values. However, the extent to which these feelings are based on underlying values is unclear because these values, difficult as they may be to verbalise explicitly, may be genuinely important to parents in the long run.[40] If this is the case, these feelings may help guide the making of decisions in this context, which is highly sensitive to preferences. However, it can be challenging to distinguish biased feelings or intuitions from those that tap into genuine underlying parental values. Feelings may arise in the heat of the moment, be based on perceived social norms or coloured by information from a biased counsellor; such feelings are not good bases for decisions in the long run because they can overshadow other important aspects. More research is needed not only to understand how much reliance parents place on intuition or thought when coming to a decision, but also whether it is wrong to incorporate emotion in this decision.[40]

To navigate these challenges in clinical practice, parents could be allowed a little extra time. This would allow them to process the information and the overwhelming emotions arising from their first reactions, thereby developing a more balanced feeling. The delay may help them consider all relevant aspects of the decision rather than just reacting to the initial shock or stress.[41] Even under the time pressure inherent in (imminent) extreme premature birth, a little extra time may help parents to make decisions that align with their values. Another suggestion is to allow parents to talk to a significant other.[42] However,

it is not always feasible for parents to fully process and understand the situation before making a decision, so it is important for healthcare professionals to continue supporting and checking in with parents postnatally to ensure that decisions are made with care and consideration.[15]

Limitations

This scoping review had some limitations. First, the depth of our results could be limited because we extracted data from the summarised documents rather than from the original interview transcripts. Second, it was impossible to count the exact number of parents mentioning each theme or to systematically compare representations of perspectives between the groups opting for intensive care and comfort care because the raw data was lacking. Third, we may have missed some grey literature outside the healthcare databases that might have included parental perspectives. Fourth, the assembled data might have been biased; cultural bias might have been present because most of the studies were conducted in the USA, or a bias might have existed towards intensive care treatment because most parents featured in the selected literature either chose intensive care treatment or made no clear, recorded decision. Finally, the widespread timeframe of parent interviews -- some were interviewed before the premature birth, some years afterwards -- may have had an impact on the perspectives parents considered important.

Conclusion

This review highlights common perspectives that affect parents' decisions at the limit of viability. An increased understanding of parental perspectives and their underlying values can improve the clarification values as part of shared decision making. Barriers should be minimised and facilitators leveraged to promote and improve the clarification of values in prenatal counselling. This may improve prenatal counselling and promote value-congruent decisions, a key goal in patient-centred care.[24]

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Appendix s1: electronic search strategies (last updated 15th april 2022)

Pubmed search

("Fetal Viability"[Mesh] OR "Infant, Premature"[Mesh] OR "Infant, Very Low Birth Weight"[MeSH] OR "Premature Birth"[MesH] OR VLBW[tiab] OR ELBW[tiab] OR EPI[tiab] OR ((viability[tiab] OR viable[tiab] OR periviab*[tiab] OR prematur*[tiab] OR preterm*[tiab] OR Pre-Term*[tiab] OR Pre-Matur*[tiab]) AND (baby[tiab] OR babies[tiab] OR birth*[tiab] OR childbirth*[tiab] OR neonat*[tiab] OR infant*[tiab] OR newborn*[tiab] OR child*[tiab]))) AND

("Decision Making"[mh] OR "Counseling"[mh] OR Decision making[tiab] OR Counseling[tiab] OR Counselling[tiab] OR "Withholding Treatment"[mh] OR "Resuscitation"[mh] OR "Intensive Care, Neonatal"[mh] OR Withholding treatment*[tiab] OR Resuscitat*[tiab] OR Neonatal intensive care[tiab] OR Palliati*[tiab] OR Comfort care[tiab] OR Active care[tiab] OR Active treatment[tiab] OR NICU[tiab] OR Neonatal care[tiab]) AND

("Parents"[mh] OR "Pregnant Women"[mh] OR Parent*[tiab] OR Father*[tiab] OR Mother*[tiab] OR Pregnant woman[tiab] OR Pregnant women[tiab] OR Maternal[tiab] OR Paternal[tiab] OR Parental[tiab]) Filters: from 2010 - 2022

This search string was adapted to each database.

Table S2 characteristics of the included articles

#	Authors	Year	Country	Aim of study	Study population and sample size	Methodology	Timing of researching the parents	*Extracted key findings (parental perspectives) concerning our study objectives*
1	Moro et al	2011	USA	To describe parents', nurses' and physician's perspectives on how parents make life support decisions for extremely premature infants prenatal through end-of-life period	Five mothers, four physicians, three registered nurses and one neonatal nurse practitioner All mothers gave birth between 23^0 and 24^5 weeks of GA of a liveborn infant who died later	Collective case study design using interviews and medical charts, single centre	Prenatal and postnatal 'little after birth' The interviews of end-of-life decisions were taken weeks to months after the death of the infant	Hope for survival Prevent pain and suffering Everything done Hope (general)
2	Young et al	2012	Canada	To gain insight on current practices from those most affected by the decisions made in the delivery room – the parents of the extreme premature babies	Ten mothers and six fathers of extremely premature infants (23-26-week of GA) who survived	Qualitative study using semi-structured interviews, single centre	All interviews <4 years after birth, except one	Potential complications of prematurity Suffering of their infant If they had known 'what was in store' would not have proceeded resuscitation
3	Roscigno et al	2012	USA	To report and evaluate parental and Healthcare providers descriptions of hope following counselling of parents at risk of delivering an extremely premature infant	40 mothers who were hospitalized for a threatened preterm delivery <26 week of GA, 14 of their partners and 71 healthcare providers (physicians, registered nurses and neonatal nurse practitioners)	Data was extracted from a (qualitative) longitudinal multiple case study using semi structured interview guides, multicentre	Prenatal and postnatal 'little after birth' Interviews about end-of-life decisions were taken weeks to months after death	The meaning of a child with a disability Hope for survival Religion (Gods hands), spirituality and faith Hope for a 'good outcome' Experiences of parents

Table S2 Continued

#	Authors	Year	Country	Aim of study	Study population and sample size	Methodology	Timing of researching the parents	*Extracted key findings (parental perspectives) concerning our study objectives*
4	Pepper et al	2012	Canada	To describe and understand the decision-making process for parents whose infants were born and survived at the extremes of prematurity at 24 to 26 weeks' gestation	Seven parents representing five families	Qualitative, interpretive description, semi-structured interviews	Postnatal, not clearly identified how long after birth	Potential handicap Percentage for complications really high Let god decide, put faith in something else
5	Kavanaugh et al	2014	USA	To outline parental descriptions of extended family involvement and support surrounding decision making for their extremely preterm infant	54 parents; 40 mothers and 14 fathers of extremely premature infants 22-25^{6}-weeks of GA	Collective case study using data extracted from a large, longitudinal multiple collective case study design using semi-structured interviews	Prenatal and postnatal little after birth The interviews about end-of-life decisions were taken weeks to months after the death of the infant	Advice 'up to God' can be hurtful / not valuing life Rely on (relatives') Experiences of parents
6	Kavanaugh et al	2015	USA	To describe how parents at risk of delivering prematurely (<26 GA) interpreted the quality of their interpersonal interaction with Healthcare providers	54 parents; 40 mothers and 14 fathers of extremely premature infants 22-25^{6}-weeks of GA	Secondary analyses of data extracted from a large, longitudinal multiple collective case study design using semi-structured interviews	Prenatal and postnatal 'little after birth' The interviews about end-of-life decisions were taken weeks to months after the death of the infant	Doing what is right, what is natural hope Infants' best interest (versus family's interest)

Table S2 Continued

#	Authors	Year	Country	Aim of study	Study population and sample size	Methodology	Timing of researching the parents	*Extracted key findings (parental perspectives) concerning our study objectives*
7	Eves et al	2015	USA	To highlight how bias may undermine the Healthcare providers ability to meet their obligation to enhance parent's autonomy and the moral distress they may experience when parental values do not align with their own	1 woman, 22^{3}-weeks pregnant, at risk for delivering prematurely	Case report	Prenatal	A degree of disability is inhumane Effect on family
8	Hendriks & Abraham	2017	Switzerland	To explore parental attitudes and values in the process of end-of-life decisions of extremely preterm infants (<28 weeks of GA)	Seven couples, five mothers and one father (n = 20) of extremely preterm infants (<28 weeks of GA) who were born alive and died in the delivery room or NICU	Qualitative study using in-depth, narrative interviews with semi-structured questions to clarify specific themes, single centre	Timeframe of 1-2 years after the infant's death	Protect against burden of NICU-treatment/prevent suffering Try everything
9	Berman et al	2017	USA	To analyse the different available ethical options to Healthcare providers and the impact those have on parents and their infant	One mother, 24 weeks pregnant, delivering prematurely	Case report	Prenatal	Caring for a disabled child Financial consequences
10	French	2017	USA	To describe different conversation the parents had with their healthcare providers about their daughter been born at 23^{+6} weeks of GA	One mother whose daughter was delivered at 23^{6} weeks of GA	Case report	Postnatal, not clearly identified how long after birth	Risk for long term morbidity Effect on marriage of hope for future children, medical debt To protect infants future

Table S2 Continued

#	Authors	Year	Country	Aim of study	Study population and sample size	Methodology	Timing of researching the parents	*Extracted key findings (parental perspectives) concerning our study objectives*
11	Geurtzen et al	2019	Netherlands	To analyse parental preferences in prenatal counselling regarding the extremely premature infant	13 (pairs of) parents who experienced an extreme premature birth (both survivors and non-survivors) at 24 weeks of GA	Qualitative study using semi-structured interviews, multicentre	Interviews were taken 2-5 years after the counselling	Long term morbidity including QoL, participation in society, physical disabilities, mental disabilities, behavioural problems, No wrong or right, Risk-assessment for your infant and family Short term: length and intensity of (NICU) stay and complications Survival – mortality, To protect your baby, To take responsibility for your infant What you can handle as a parents
12	Edmonds et al	2019	USA	To examine prospective parental perceptions of management options and outcomes regarding threatened periviable delivery and the value's they apply in making a decision antenatal	54 prospective parents hospitalized for threatened periviable birth (22^0 to 25^6 weeks of GA)	Qualitative study, using data of prenatal interviews which were a part of a larger study, multicentre	Prenatal	Disability Healthy infant Protect against burden of NICU-treatment/ concert about pain and suffering Faith Responsibility for decision Doing what was best Giving a fighting chance Experiences

Table S2 Continued

#	Authors	Year	Country	Aim of study	Study population and sample size	Methodology	Timing of researching the parents	*Extracted key findings (parental perspectives) concerning our study objectives*
13	Lynch et al	2019	USA	To help Healthcare providers determine how to support their patients in medically complex and emotionally laden decisions by understanding parental experiences of their periviable deliveries	Ten women who delivered between 22^0-25^0 weeks of GA	Qualitative study using open-ended, semi-structured interviews, single centre	24h-12 days after delivery	Survival Families interest versus infants interest Try everything What is best for her
14	Ursin & Syltern	2019	Norway	Discussing the role of parents in neonatal decision-making, based on the following research question: Should parents decide whether to provide lifesaving treatment when their child is born at the limit of viability?	12 parents of children born at 23–24 weeks of GA, one at 34 weeks of GA (threatening birth at 22 weeks of GA)	Qualitative study using structured interview format, multicentre	Postnatal, not clearly identified how long after birth	Not wanting this life for the infant Survival Long term outcomes for the family system Everything done Responsible for decision/instinct of saving/protecting your child Wanting the best for the child
15	Jager et al	2020	USA	To explore the language pregnant woman and important others use when discussing comfort care as an option to treat their extremely premature infant	30 pregnant woman (between 22^0 and 24^6 weeks of GA) and their 16 important others	Secondary analysis of data collected as a part of prospective qualitative and quantitative study, multicentre	Prenatal, interviews were taken after receiving antenatal consultation from the NICU-team	Not wanting the child to have a low quality of life Chance of survival Protect against burden of NICU-treatment; not be in pain and suffering Having faith Not giving up hope Giving the baby a chance

Table S2 Continued

#	Authors	Year	Country	Aim of study	Study population and sample size	Methodology	Timing of researching the parents	*Extracted key findings (parental perspectives) concerning our study objectives*
16	Haward et al	2021	USA	To explore parental experiences of extremely preterm infant loss in the delivery room an perspectives about prenatal consultation	13 participants who experienced loss of their infant	Qualitative study using semi-structured interviews, multicentre	Postnatal, not clearly identified how long after birth	Long term outcomes for the child/(future) quality of life Survival Protect against pain and suffering Long-term outcomes for the family system Faith Hope versus realism Doing what is right Experiences
17	Tucker Edmonds et al	2021	USA	To explore perceptions of pain/ suffering, disability and coping by race among pregnant women facing the threat of a periviable delivery	30 pregnant women facing the threat of a periviable delivery (22^0-24^6 weeks of GA)	Qualitative study using semi-structured interviews, multicentre	Prenatal	Long term outcomes for the child/concerns for (long term) quality of life Survival Protect against burden of NICU-treatment Faith Everything done Giving a (fighting) chance/strength to fight

Abbreviations: GA: Gestational Age, NICU: Neonatal Intensive Care Unit, ELBW: Extremely Low Birth Weight

Intermezzo A:

How we handled our son's birth at the limits of viability after an unexpected pregnancy

Dirk-Jan Berken and Hiske van Dam

Acta Paediatrica, 2023

Parental perspective

In this paper, Dirk-Jan and Hiske, the parents of an infant born at 24 weeks of gestation, provide an insight into their experiences of the birth and making decisions at the limit of viability. They were faced with the risk of an extremely premature birth at 22 weeks of gestation. The delivery miraculously stalled, and the limit of viability moved closer. The couple received prenatal counselling about the treatment options after birth, which were initiating intensive care treatment or comfort care. Together with physicians, they made the decision to initiate intensive care treatment if the infant was born in the grey zone. Different values were considered important in their lives during the decision-making process.

Dirk-Jan: We suddenly discovered that Hiske was 18 weeks' pregnant, even though she had been told that she was infertile. Soon after, she went into premature labour and was admitted to hospital at 22 weeks of gestation. We were told Hiske would give birth that same day and that nothing could be done for the baby. Miraculously, the birth stalled, Hiske's contractions stopped, and the limit of viability came closer. Before we could begin to process what was happening, we were meeting the neonatologist and were presented with some ethical dilemmas. How could we decide between active treatment or comfort care?

Hiske: We started with a tough, but honest, conversation with the neonatologist about our baby's chances and risks after premature birth. We had to prepare for a difficult journey with an unknown outcome. This experience was completely new to us because we did not know what was going to happen. During this period, hope and fear alternated and there were many setbacks, as well as small silver linings. We relied on ourselves and each other and stayed hopeful, even though we felt very vulnerable. We struggled through this situation as a couple and envisioned what the future would bring us. You think about what the outcome will look like and deal with the confusion of so many different emotions. It would have been so easy to drift away from each other as we went through this experience, and we had to keep on finding each other again. We both had our own fears and sorrows and our own way of dealing with them.

Dirk-Jan: During counselling we received a link to a digital information decision aid '*Keuzehulp vroeggeboorte*'[1], where we could find additional information. Given the intensity of the conversation, we wanted to make sure we understood everything correctly. We were silently in our own world of thoughts for a brief moment of time in our hospital room, processing the given information that had been shared with us in such a short time. During this whirlwind of intense emotions and thoughts, we had to go through statistics about complications, risks of permanent damage and chances of survival. There were so many questions. How would our little boy fight this and win? Could and did we want to deal with the most severe scenarios? What would our life be like? We expressed our thoughts, fears and wishes to each other and were mostly on the same page. This was the beginning of an extremely difficult process, which could take months and we knew that our son may not

survive. We had the second appointment the next day, when we had barely pulled ourselves together and recovered from the first conversation with the neonatologist. We explained our wishes to the team, who took the time to listen and to answer all our questions.

Hiske: This big decision could only be made together, and it was emotionally overwhelming. We knew that we could not make this decision alone without discussing it with each other and without mutual support. First, we had to decide what we each wanted and then move forward together. We needed each other during this tough process. It was immediately clear to us that we wanted to go all the way and wanted all the medical help available. Becoming pregnant had initially seemed impossible, so the fact that I was pregnant was a miracle on itself. Therefore, I felt I could not deny our son a fighting chance. We had hope, as we knew that life could consist of misery, but also miracles. We knew that if there were too many complications, and it all became too much for our son, we only had one option left. As much as this would devastate us, we would be open to withdrawing intensive care if the treatment was not proportional with the prognosis anymore. However, it was not up to us to decide this for him while I was still pregnant.

Dirk-Jan: The feeling that we had to give our son a chance prevailed. We were also realistic enough to say farewell to him if his complications meant he had a prognosis of an undignified existence. Hiske was admitted to the maternity ward, and, due to our previous experiences over the weeks, we had enough confidence that the doctors would give us good advice and helping us decide if severe complications arose. We agreed with the neonatologists that we would receive clear and honest advice to withdraw intensive care if everything had been done from a medical perspective or if our son developed complications that led to such severe disabilities that it would leave him with an undignified existence. We agreed we would follow their advice. After his birth, we had multiple conversations about the chances of our son's survival in the neonatal intensive care unit. At one point he was very sick, and a positive outcome seemed unlikely. We agreed to wait two days to see if there was a chance to recovery, but if there was not, we would make a decision with the team to withdraw his treatment and say our goodbyes. Feeling part of the team and being able to discuss things openly with them helped us to make these difficult decisions together.

Our son was born at 24 weeks and 3 days of gestation. He weighed 575 grams at birth. After 107 days in the neonatal intensive care unit, he was transferred to the post intensive care unit. He came home with oxygen and tube feeding 157 days after he was born. His first year of life was dominated by the medical world: lots of checks, slowly reducing his oxygen, switching him to normal food, planned and unplanned operations and more follow-up visits. But on the positive side, he made small steps forward in his development at his own pace and required less and less input from the medical world. Meanwhile, we celebrated his first homecoming day and now our son is developing more and more. We are very grateful to experience this with him.

To parents and healthcare professionals

The principle of shared decision-making at the neonatal intensive care unit and our strong belief in our own decisions and reasoning gave us a certain empowerment. This empowerment helped us feel in control as much as possible, in a situation where control seems so often far away. It gave us the feeling of having a bit of grip on the situation, which you can hold on to during this unbelievable journey where you must remain standing till the end. We do believe we made the decision for our son, within the medical constraints and possibilities told by the neonatologist who did not influence our decision personally.

Based on these experiences, our advice to healthcare providers would be to always be honest and keep repeating information to the parents. Make sure parents feel heard and give them space to think over a tough decision and respect that choice, even if you would have made a different one. In case, time is sensitive or in the line of events, explain everything that happens, will happen en will be done, not only before birth but also directly after.

To the parents, listen to your feelings and your heart and dare to face the truth, keep asking questions repeatedly till it is clear to you. Stand strong by the decision you made and never blame yourself for anything, nor regret the choices you made.

Reference:

1. Van den Heuvel, J.F.M., Hogeveen, M., Lutke Holzik, M. et al. Digital decision aid for prenatal counseling in imminent extreme premature labor: development and pilot testing. BMC Med Inform Decis Mak 22, 7 (2022)

Chapter 3

Perspectives of extremely prematurely born adults on what to consider in prenatal decision-making: a qualitative focus group study

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Abstract

Objective: A shared decision-making (SDM) approach is recommended for prenatal decisions at the limit of viability, with a guiding role for parental values. People born extremely premature experience the consequences of the decision made, but information about their perspectives on prenatal decisions is lacking. Therefore, this study aims to describe their perspectives on what is important in decision-making at the limit of viability.

Design: Semi-structured focus group discussions were conducted, recorded, and transcribed verbatim. The data were independently analysed by two researchers in Atlas.ti.

Results: Four focus groups were conducted in the Netherlands, with 5-6 participants each, born between $24^{0/7}$-$30^{0/7}$ weeks gestation in the period between 1965-2002. Considering their personal life experiences and how their extremely premature birth affected their families, the participants reflected on decision-making at the limit of viability. Various considerations were discussed and summarized into the following themes: anticipated parental regret, the wish to look at the baby directly after birth, to give the infant a chance at survival, quality of life, long term outcomes for the infant and the family, and religious or spiritual considerations.

Conclusions: Insights into the perspectives of adults born extremely premature deepened our understanding of values considered in decision-making at the limit of viability. Results point out the need for a more individualized prediction of the prognosis and more extensive information on the lifelong impact of an extremely premature birth on both the infant and the family. This could help future parents and healthcare professionals in value-laden decision-making.

Background

When an extremely premature birth is imminent, a prenatal decision must be made whether to start early intensive care (EIC) or palliative comfort care (PCC).[1] Accurately predicting individual outcomes is difficult and the evaluation of the estimated prognosis is value laden.[2,3] Therefore, shared decision-making (SDM) is recommended which includes the elicitation and incorporation of parental values.[4] Various parental perspectives are known to be important in decision-making, such as long-term outcomes, survival and the impact on the family-system.[5] Parents may choose EIC to "*give a chance*" and to "*do everything possible*",[6,7] while others may choose PCC to "*avoid a life of challenges and potential handicaps*".[8,9]

Adults born extremely premature experience the consequences of their extremely premature birth[10] and witness the impact on their families.[11] Although the importance of reporting long-term medical, psychological and social outcomes are being increasingly recognized,[12] the perspectives of these individuals on the prenatal decision-making process are still unknown.[5] Although parents are the surrogate decision-makers for their infant, understanding the perspectives of adults who were born prematurely is valuable in that it represents how the actual patients ultimately reflect on this decision. To give voice to the individuals most affected by these decisions, this study aims to describe the perspectives of extremely premature born adults on what they believe is important in decision-making at the limit of viability. This may support healthcare professionals and future parents in SDM.

Methods

TINY-1-study

This qualitative study was conducted as part of the TINY project (Towards Individualized care for the Youngest) by researchers from the Leiden University Medical Centre; Erasmus Medical Centre, Rotterdam; and Radboud University Medical Center Nijmegen, in the Netherlands. Ethical approval was obtained from the Medical Ethics Committee Leiden-Den Haag-Delft (N21.147, November 2021). Topics of interests are (1) guidelines, (2) personalization, and (3) values in decision-making at the limits of viability. This article presents the results of TINY-1 on values important in decision-making.

Study design and participants

Focus group discussions were conducted, aiming for a limited number of participants in each group to create a safe environment but still facilitate discussion. Participants were recruited through the Dutch patient association Care4Neo and social media (e.g., LinkedIn). Participants included had to be born extremely premature, >18yr of age and able to verbally express themselves well. Individuals who were interested to participate contacted the researchers via email. Information and informed consent forms were sent. All individuals who signed up and met the inclusion criteria, were included in the study. After signing up, a questionnaire for background information followed to collect demographic and

health-related information. Participants were divided into focus groups, ensuring diversity in age, gender and health status. An individual meeting was planned with each participant around one week before the focus group discussion to elaborate on the research project's background and aim, and to answer any questions. Information was shared, including the number of participants, the structure of the focus group discussions, the duration and other relevant logistical details. After the focus group discussions, an individual debriefing meeting was offered as aftercare to all because of the potential impact the discussions could have. We discussed how they participants experienced their participation in the focus group discussion. A 30-min meeting was held with 15 of the 23 participants, who all had a positive experience.

Data collection

Due to COVID-19 restrictions, the focus group discussions were held through video conferences. All were moderated by the same researchers LP and AB, with backgrounds in philosophy and bioethics (LP) and medicine (AB). At each session, a third researcher (neonatologist (RG) or obstetrician (JV)) was present to answer questions but not participate in the discussion.

An interviewguide was developed based on a review about what is known in literature on this subject.[5] It comprised (I) general instructions (aim, rules, and expectations) and (II) open-ended questions with follow-up probes for facilitating discussion (*appendix 1*). Treatment options at the limit of viability were explained, just as the aim to use an SDM-approach and incorporate parental values in decision-making. Open-ended questions were asked on important values, perspectives, or arguments to take into account when making a treatment decision. Finally, a figure representing an overview of parental perspectives gleaned from literature was shown and participants' comments were explored (*chapter 2*).[5]

Data analysis

The sessions were recorded and transcribed verbatim. Results were analysed and coded independently by two authors (AB, LP) in Atlas.ti, using thematic content analysis. The codebook and analysis were discussed and adjusted in multiple rounds until agreement was reached (AB, LP, RG, EV) (*appendix 2*). Findings were reported following the COREQ-criteria (*appendix 3*).[13] Every quote in the results section is accompanied by a number (session) and letter (participant).

Results

Focus group and participants' background

In January and February 2022, four focus group discussions were conducted with 5-6 participants per group (n = 23). With the aim of diversity each group was composed of participants with differences in the year of birth, gender and the self-reported long-term consequences. Characteristics and self-identified long-term consequences were reported in *Table 1* and *2A*. The participants in this study were born between $24^{0/7}$-$30^{0/7}$-weeks of

gestation in the period between 1965 and 2002. The differences in outcome of our participants, born within a 37-year time span, could be partially explained by the range of potential outcomes of extreme prematurity but also by differences in neonatal treatment over time. Since the major advances in management of extremely premature infants, the long-term consequences of our participants are also reported broken down by their year of birth in *Table 2B*. No significant differences in experienced consequences are observed between the groups. Most of them experienced challenges of being born extremely premature influencing their lives as adults. Various consequences were reported, such as brain injury, cerebral paresis, bronchopulmonary dysplasia (BPD), visual impairment and hearing loss, as shown in *Table 2A* and *2B*. In some of these cases, the experienced consequences led to (e.g.) inability to work. Despite these consequences, most participants expressed how '*they got lucky*', and that '*it could have been worse*'. They were aware that other individuals born at the same gestational age suffered from more severe complications or did not survive.

Table 1 Self-reported sociodemographic and clinical characteristics of the participants.

Patient characteristic	**N = 23**
Participants	
Man	5
Woman	18
Born at gestational age	
24^{+0}-25^{+6}	3
26^{+0}-27^{+6}	13
28^{+0}-30^{+0}	7
Born between	
1965-1980	4
1981-1990	9
1991-2002	10
Education	
Secondary school / Secondary vocational education	5
Higher professional education	10
University education	8
Religion	
Christian	6
No religion	17
One of multiples	
Yes (twins)	3
No	20
Location premature birth	
Academic hospital	14
General hospital	6
Foreign hospital / at home	3
Long-term consequences of premature birth	
Yes	15
Possibly	2
No	6

Table 2A Self-identified and reported long-term consequences of their extreme premature birth

Consequences	N = 17
Cognitive	
Cognitive / learning disability / problems at school / brain injury / memory disorders	5
(Neuro)motor function	
Problems with moving (due to hypo/hypertonia) / cerebral paresis	9
Psychosocial	
Concentration problems / ADHD*	8
(symptoms of) Autism Spectrum Disorder	2
Other psychosocial problems	1
Physical	
Vision / hearing problems	7
Respiratory problems	7
Reduced immunity / susceptible to infection	5
Easily fatigued	5
Growth restriction	4
Eating/feedings problems	4
Intestinal problems	3
Other self-described consequences: Feeling misunderstood, attachment problems, anxiety disorder / performance anxiety, insecure / the need to proof themselves, stimulus processing problems	

*ADHD = Attention Deficit Hyperactivity Disorder

Important considerations in decision-making at the limit of viability

The participants in this study agreed with the SDM-approach as recommended in clinical guidelines and emphasized the importance of involving parents and their values in the decision-making process. Participants' explorations on values important in decision-making were multidimensional, reflecting on factual risk information as well as feelings and assumptions about care for extremely premature infants. The following themes were identified: anticipated regret or guilt, looking at the child after birth, giving a chance at survival, quality of life, consequences of EIC-treatment and religion and spirituality.

Table 2B Self-identified and reported long-term consequences of participants' extreme premature birth by year of birth

Year of birth	Gestational ages	Reported long-term consequences of participants born in the reported period of time
<1980[1]	$26^{+?}$, $27^{+?}$, 30^{+0}	Cognitive / learning disability / problems at school / brain injury / memory disorders Problems with moving Reduced immunity / susceptible to infection Respiratory problems Intestinal problems (symptoms of) Autism Spectrum Disorder Stimulus processing problems Attachment problems
1980-1990[2]	$26^{+?}$ (2), 26^{+3}, 26^{+4}, 27^{+0}, $27^{+?}$, 28^{+0}, $28^{+?}$, 28^{+5}, 29^{+0}	Cognitive / learning disability / problems at school / brain injury / memory disorders Problems with moving/ Cerebral paresis Easily fatigued Vision / hearing problems Eating/feedings problems Respiratory problems Intestinal problems Reduced immunity / susceptible to infection Growth restriction (symptoms of) Autism Spectrum Disorder Feeling misunderstood Insecure / the need to proof themselves *Two persons born between 1980 and 1990 reported no consequences.*
1991-2002[3]	24^{+6}, 25^{+0}, 25^{+3}, 26^{+0}, $27^{+?}$ (2), 27^{+0}, 27^{+3}, $28^{+?}$, 29^{+6}	Cognitive / learning disability / problems at school / brain injury / memory disorders Problems with moving Vision / hearing problems Growth restriction Respiratory problems Reduced immunity / susceptible to infection *Four persons born in 1991 or later reported no consequences.*

1. 1970-80: Advances in the respiratory management of the premature infant; CPAP, discovery of application of prenatal corticosteroids[30]
2. 1980-90: First successful administration of surfactant to a newborn, family centered care expanded, Nitric Oxide for persistent pulmonary hypertension of the newborn (PPHN)[30]
3. Before 2010, the Dutch threshold of viability was at 25 weeks.

Anticipated regret or guilt

Participants imagined that the decision on care for extremely premature infants may be influenced by anticipated regret or guilt, particularly in choosing EIC-treatment over PCC, as one participant noted: palliative care cannot be undone". They acknowledged the uncertainty surrounding individual outcomes and prognosis, and the difficulty parents may have in making this decision. Participants sympathized with their parents for being in the situation of imminent extremely premature birth, certainly not blaming them for the decision they made.

Box 1: Quotes 'Anticipated regret or guilt'

"I can also imagine that some parents may feel guilty if an infant does not come out of it alive or at least not unscathed." (4A)

"As a parent, you cannot make a wrong choice. You do what you think is right." (2D)

Looking at the child after birth

In each session, participants suggested to make the decision based on the infant's condition immediately after birth. They emphasized the importance to consider EIC if the infant showed a will to live. Participants opted to look for signs such as movement, crying or discomfort.

Box 2: Quotes 'Looking at the child after birth'

"Look at movements, but also how comfortable the baby is. (...) How does the baby breathe in life? (...)" (4C)

"The activity of the infant, so whether it is moving or floppy. (...) whether it is trying to stay alive. I think you can tell a lot from that. (...)" (4A)

Giving a chance at survival

Participants imagined parents would typically want their infant to survive and to initiate treatment when there was a chance or hope on survival. They expressed that parents may want to seize the chance to see their infant grow up. However, participants considered it important that parents are informed about what an infant must go through to survive after extremely premature birth and take this into account. They emphasized that survival should not be pursued at all costs, and if the infant is not viable or the treatment is disproportional, palliative care should be considered. So, participants discussed that parents should be counselled about potential later decision moments regarding withdrawal of EIC-treatment if things changed for the worse.

Box 3: Quotes 'Giving a chance at survival'

"...a physician should really say what the chances of survival are, but maybe it is also good for parents to know what it takes to survive. (...) [My parents] found it quite difficult to see what I had to go through. They were not told what it would take" (3A)

"If your baby suffers severely and it becomes very heavy to endure, [the healthcare professionals] supposedly will not say: we will continue to the bitter end." (2A)

Quality of life

Quality of life (Qol) was an important theme discussed by the participants, but difficult to define. They were unsure how to determine what a good Qol is and by whom this should be determined. However, according to one participant QoL should not be determined based on potential physical handicaps.

Box 4: Quotes 'Quality of life'

"I find 'quality of life' a bit difficult. I agree with the words. (...) [but], what is quality of life?" (3D)

"*Why, who decides when life is fun or valuable? That is indeed very personal.*" (1B)

"*What you often hear people say, one of my great annoyances, is: "As long as the child can walk." Then my thoughts are: are you going to measure happiness or a child's happiness in life by what someone can physically do?*" (1A)

Consequences of early intensive care treatment

Overall, the consequences of EIC were mostly discussed in terms of lifelong consequences for the infant and the impact on the family. Several personal anecdotes and stories were shared while this topic was discussed.

Long-term consequences for the extremely premature infant

Concerns were raised about the underestimation of the consequences of being born extremely premature and the effects of being admitted to the NICU. It was agreed upon that parents should be well informed about all the long-term consequences, including physical and psychosocial challenges both in childhood and beyond, and the great impact it could have on life. Participants felt as if they were living in survival mode since their birth and their capabilities were often overestimated. One participant was at an age where she compared herself with others building a future, knowing she could never do or achieve the same as them.

From their perspective, more research is needed on long-term consequences, particularly the psychosocial aspects and the consequences in adulthood, so parents can be informed in more depth about the prognosis of their child.

Box 5: Quotes 'Long-term consequences for the extremely premature infant'

"A premature birth has a significant impact, psychological and emotional (...), it would be good to know that beforehand" (1F)

"I think, certainly for parents, long-term effects are not really about when the child is 30, 40, 50 years old, but more about when the child is a child?" **(1A)**

*"I did suffer from a minor motor disability afterwards, which also limited my social development, because I was less able to participate in a team sport, such as football. I certainly experienced a limitation during my high school days, but also during my student days. I could not always participate and keep up, so I missed a lot of social activities."***(2B)**

"The survival mode is always on, meaning constant turmoil in my head. (...) Not controlling all the stimuli, causing that I cannot keep up with and fully participate in society" **(2D)**

Impact on family

Furthermore, discussion about the impact of having an extremely premature infant on the family arose. The participants shared how their premature birth affected their family, especially their siblings, with examples like the absence of the parents during those first months of NICU-treatment influencing family life, how afraid a sister of one participant

was to touch her during the first years, or the guilt one participant felt towards her siblings because of all the attention she got instead of her siblings. They emphasized the importance of considering the family context in the decision-making process, and of assessing the parental capacity to handle the consequences of having an extremely premature infant. Due to the potential impact on the family, participants thought social support should be addressed during counselling. Besides, parents' financial situation should be taken into consideration, as they may have to financially support their child in the future.

Overall, participants emphasized that while family impact should be considered during the decision-making process, this should not be the ultimate deciding factor. Rather, it should be discussed during counselling to prepare parents for the potential impact of having an extremely premature infant and to assess their needs for support.

Box 6: Quotes 'Impact on family'

"As my mother says to this day: "You are and will remain a child I worry about". And [my two sisters] aren't. I feel badly about that for them (...) It feels like the attention mostly goes to me, while my sisters deserve it just as much." (2D)

"*at such a moment you may forget that it is also really intense mentally for yourself. That you also should be able to handle it, as a parent."* (3D)

"*...you also should ask - in both the positive and negative scenarios - what kind of social support there is, because you just can't do it alone and you just need your resources."* (1C)

"*I am lucky my parents can financially support me, because I cannot pay for my living on my own due to the medical support I need*." (2D)

Religion and spirituality

The role of spirituality was expressed as an important factor. The role for religion was only speculated on, as it was not of personal importance for them.

Finally, after showing the presented figure of parental considerations extracted from literature (*chapter 2*), the participants mostly confirmed or expanded upon the perspectives that had already been discussed spontaneously.

Discussion

Our study offers unique insights into the perspectives of adults who are extremely premature born on what they themselves consider as being important in decision-making at the limit of viability. This group of adults born extremely premature has firsthand experience of the consequences of premature birth and witnessed the impact on their families. Participants suffered different gradations of consequences of their extremely premature birth. These outcomes ranged from experiencing one or more issues in domains such as (neuro) motor function, cognition, and psychosocial well-being, to experiencing no consequences whatsoever. Based on this diversity of experiences, they identified important issues to be considered during prenatal decision-making. Participants were grateful for being in-

volved in research and for being heard, since they feel their expertise is underrepresented. Therefore, it is important to value and acknowledge their perspective, which could help in further policy development.

The perspectives of the adults born extremely premature placed unique emphasis on perspectives known from previous research. Our results substantiate (I) the wish to look at the child directly after birth to give a more individual prognosis, and the results provide new insights into (II) the impact on the family, and (III) the need for parents to consider the fact that extreme prematurity is a lifetime diagnosis with its challenges. These results can help in value-based counselling as part of personalized counselling and SDM.

First, the wish to "look at the child" and to use this information to decide, may reflect the hope for an uncertain and general prognosis to become a more individualized prediction of the outcome. However, it is nearly impossible to predict outcome based on first impressions and Apgar scores, there is no evidence that first impressions can be used to postpone the decision whether to initiate life sustaining treatment or not till the baby is born.[14] Parental hope on the usefulness of first impressions should be refuted. Furthermore, it is importance to address uncertainties and the impossibility to predict an individual outcome.[15,16] However, doctors should share what they know to provide a more individualized prediction of the outcome. For example, parents could be better guided in the process of decision-making by informing them about how various factors could influence neonatal outcomes and by providing them with information on postnatal predictors of prognosis, including any potential treatment limitations.[16-18]

Secondly, participants wished the impact of extremely premature birth on the entire family to be considered in prenatal decision-making, particularly on siblings and the financial consequences for the family. Research has shown that the effects of a premature infant with a disability can have substantial impact on the family[11, 19, 20], especially the negative consequences of reduced parental attention for siblings[11, 21], and feelings of loyalty and responsibility toward the prematurely born infant.[21] By discussing the impact of premature birth on families, parents can incorporate this into their decision-making process and determine whether additional support for the family is needed.

Lastly, participants emphasized the importance of informing parents more about the long-term consequences of extremely premature birth. While the consequences during childhood are widely recognized by healthcare professionals and parents, our participants emphasized the lifelong consequences beyond childhood, as well as the lack of aftercare later in life. Research on the consequences and outcomes of adults who were born extremely prematurely is increasingly available.[10,22-28] Studies demonstrate a higher risk for poor social outcomes in adulthood[24,25,29] and an increased risk for long-term morbidities.[27] Participants showed that in their individual cases, their parents felt unprepared for these long term issues. It is unknown why neonatologists do not put emphasis on functional

long-term outcomes in prenatal counselling. It may be that they are not sufficiently aware of these long-term consequences, or that they do not consider it a priority topic, or maybe parents do not consider it important enough and consequently focus on the present reality.[5] Participants want future parents to be informed about the challenges their infant may encounter in healthcare, school, work and personal life, which may continue or arise beyond childhood.[10,27,28]

However, presenting data on long-term outcomes in adulthood comes with an inherent dilemma for HCPs, as data is inherently collected ages ago. Changes in patient care have occurred in the evolving field of neonatology.[30] Treatments that are given today may have positive or negative influence on long-term consequences and those can only be known through long-term follow-up. It is important to acknowledge this complexity while counselling parents about the long-term outcomes beyond childhood. Nevertheless, prenatal treatment decisions on resuscitation must to be made based on the best available information. Furthermore, our results merely show that the impact on a premature born person and his family is lifelong and even though emphasis may switch over time from one medical or psychological problem to another, the main message is to discuss the fact that the impact is lifelong and that is unlikely to change.

Therefore, it is essential to (I) discuss the potential lifelong consequences and challenges in various aspects of life while acknowledging that the information is derived from 'older' but only available data, and (II) make parents aware of the lack of follow-up beyond early childhood.[31]

Strengths and limitations

The major strength of this study is the uniqueness of participants; the prematurely born adults. However, our study also has some limitations. Firstly, the major limitation is the possible survivor bias caused by the inherent non-representative sample of participants. Obviously, only those for whom an EIC-treatment was chosen and survived could be included. Participants were only included when they had the intellectual and communicative level to be able to participate. Furthermore, it is uncertain how the heterogeneity in individuals' outcomes with regards to the level of disabilities influences their perspective (whether positive or negative) on these outcomes. Consequently, the composition of the sample also affects the results. However, our participants experienced various consequences of their extremely premature birth, like cerebral palsy or BPD. It is impossible to include non-survivors and adults with severe cognitive impairments. Additionally, recruitment through social media and the patient organization could have caused a selection bias.

A second limitation is that the study focused on participants from the Netherlands where the standard of neonatal care and societal and cultural values may differ from those in other countries. The Dutch context prioritizes quality of life[32], which may have influenced

the perspectives of the participants. Furthermore, it is a high-income country which influences the availability of neonatal intensive care.

A third limitation may be that our results are limited by reporter bias, due to the study design of online focus group discussions. This design may not always allow for a full expression of thoughts or feelings, and may have affected the group dynamics although unknown in which way. However, during the individual meetings afterwards, none of the participants reported any issues related to these limitations.

Lastly, recall bias could have limited the results by the potential misrepresentation or inaccuracy in participants' recollection of past events or experiences. However, we explored their perspective on what they now consider important based on their experiences in life and did not ask about one particular event in the past.

Conclusion

To the best of our knowledge, this is the first qualitative study with extremely prematurely born adults on what they consider important values in prenatal decision-making at the limit of viability. Their perspectives have so far been underrepresented but could contribute to improving care for (future) parents and their infants. Our study suggests that it is crucial to address the expectations and uncertainty regarding individual prognosis.[17] Additionally, the results emphasize the importance of providing parents with comprehensive information about potential consequences for both their infant and their family associated with an extremely premature birth. Extremely premature birth should be considered to be a lifelong diagnosis.[25]

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Appendix 1: interviewguide TINY-1

1. *A short introduction for the focus group*

   In short: welcoming the participants, explaining the aim of the research and the rules. Followed by a round in which the participants could introduce themselves and why they were participating.

2. *Introduction of the subject*

   In short: explaining a normal pregnancy is 40 weeks. Followed by an explanation of the grey zone, the treatment options at the limit of viability, and the decision that has to be made together with parents. Part of this decision is to elaborate what they think is important in life.

3. *Part I: Periviable guidelines & Part II: Personalization of care (not the scope of this thesis)*

4. *Part III: values*

   In this part of the focus group we want to discuss what you think is important in decision-making when extremely premature birth threatens. When there is no best choice, because advantages and disadvantages are influenced by what you/your parents/your family consider important in life, it is recommended to decide together with parents what decision is best. In such a decision, various aspects or arguments can play a role for parents and families. You can also call these values.

a) Values important in decision-making
- What arguments/values do you think should be important in making a decision regarding treatment after birth at the limits of viability?
  - o Exploring the named arguments/values/perspectives with questions like
    - What do you mean when you say [value/argument/consideration]?
    - If you say [value/argument/consideration], what should we be considering? Etc.

b) We searched the existing literature on what parents consider important in making a decision whether to initiate intensive care or comfort care after premature birth. The results we found are displayed in a figure. We are going to show the figure (*see chapter 2)* The size of the circles is based on the number of articles in which the perspective is mentioned.
- What comes to mind when seeing this figure?
- Which perspectives in the figure do you recognize, or you do not recognize? And why?

Appendix 2: codebook

Theme	Subcode	Description
Financial impact	Financially barrable?	Considering in decision-making if it is financially bearable for the family?
	Financial support parents	Considering in decision-making if parents could financially support a possible disabled child with its financially consequences
	Financially stable situation	Considering in decision-making if parents have a financially stable situation
Got lucky	Aware of miracle	Be aware of the miracle to be born healthy or not suffering from serious consequences
	Thankful for life	Thankful for the life or being a life
	Way of life	Being lucky, in context of how you live your life as a result of the knowledge you got lucky
	How it could have been	How it also could have been, for example serious disabilities
	Few consequences	Having few till no consequences of the premature birth
Give a chance	Chance of survival	Choosing intensive care treatment when there is a chance of survival
	End of life decision in the NICU	Choosing intensive care treatment with the knowledge the decision to end life support in the NICU is possible when treatment is not proportional anymore
	Try/everything done/ save	Choosing intensive care to try and do everything
Impact on family-system	Siblings	Take the impact on the siblings into account
	Context of family	Consider the context of the family
	Parental capacity	Important to judge the parental capacity, otherwise extra help is needed
	Negative	Someone mentioning this should not be considered
Individualize	Every decision is a good one	You cannot make a bad decision
	Value clarification each parent	Value clarification should be performed, with each parent on its own
	Values individual process	Forming values and having values are an individual process
	Values differ per individual	Everybody has his own values
	Which knowledge/ numbers are needed/ wanted	Individualize the knowledge you give, the number you mention based on what a individual wants to hear
Intuition	Could go wrong	Making a decision based on intuition or fully emotional, could go wrong
	More intuition than deliberation of values	Could imagine intuition plays a bigger part in decision-making, than deliberation of values

Theme	Subcode	Description
	Feeling of a mother/ instinct	It is just a feeling of a mother, a primal instinct
	Peace	Peace is necessarily
Look at the child	Survival instinct	Making the decision based on the instinct to survive the child shows
	Situation infant post-partum	Making the decision based on what the child shows after birth
	Fighters	Making the decision based on if the child shows it wants to fight for life
	Examples of factors	Examples of factors that should be looked at after birth to estimate the will to live
Protect against burden of short- and long-term outcomes (LTO)	Short term outcomes	Mentioning short term outcomes to consider (NICU-treatment)
	LTO - possible suffering	Considering the possible suffering for the child resulting from long-term consequences
	LTO – not an easy life	Considering long-term outcomes which could lead to a difficult life
	LTO – consequences for the child	Considering consequences for the child
	LTO – 'kasplantje' (=dutch expression meaning vegetable)	Considering the prediction of being a 'kasplantje'
	LTO – difficult to predict	Long-term outcomes are difficult to predict
	LTO – future research	Future research has to be done in this field
	LTO – consequences for the adults	Considering consequences for adults who were born prematurely
	LTO – wrong prediction	Be careful with predicting outcomes because it could be wrong
	LTO – educate parents	Inform parents about the possibilities of long-term consequences
	LTO – what is acceptable	What are acceptable outcomes? Differs between individuals?
Quality of life	Context of a healthy life	Quality of life in the context of a healthy life
	How to determine	Quality of life is important, but how do you determine what is quality of life and who is going to do that
	Individual	It differs per individual what quality of life is
	Quality of life	Only quality of life was mentioned as important
	Pleasure in life	The possibility of pleasure in life should be considered as part of quality of life in decision-making

Theme	Subcode	Description
	Unpredictable	Very hard to predict if a child would have a good quality of life, but it still should be considered with the available knowledge
	Prediction	Predicting quality of life with the available knowledge
Quote	(Theme to use with)	Quote
Taking control	Include in decision-making	Parents have to be included in decision-making
	To take control	Considered important that parents have control in decision-making
	To take away control	Be aware of things that could take control away from parents, like not clarifying values
	Which part in decision-making	Important to include parents in decision-making, but always ask which part they want to play
Religion	No active termination of life	Religions could say active termination of life is not acceptable
	Values formed out of religion	Could be imagined that values based on religion could be important for some parents
Anticipated guilt/regret	Possible suffering	The consideration of anticipated guilt about the suffering of a child when faced with complications after birth
	Wrong choice	The consideration of anticipated guilt when making the wrong choice, either intensive care or comfort care
	Different perspective of the child	Different views of parents and the child related to the possibility of regret or guilt
SDM	Afraid to make the wrong choice	Being part of the decision, could make parents afraid to make the wrong decision
	Uncertainty	Making a decision together while there is so much uncertainty
	Hardest decision	It is the hardest decision there is
	Process of decision-making/transparency	Include parents in the process of decision-making, be transparent
Social support	Social support	Considering social support in the decision-making
	Support from environment	Considering the social environment of parents in the decision-making
Spiritualty	It has to be like this	To be alive, it has to be like this
	Connection with the child	Estimate which decision you have to make based on the connection with your child
Survival	Hope to survive	Hope on survival
	Chance of survival	The chances of survival
	Despite outcomes/ consequences	Survival at all, despite which outcomes/consequence there are, it is all acceptable
Responsibility	Advocate for the child	Feeling responsible for their child and therefore fighting/advocating for them

Intermezzo B:

‘Vroeggeborenen willen zorg op maat: ‘levenslange gevolgen’ (In Dutch)

Andre Haccou*, Jessy de Cooker*, Angret de Boer

**Andrea Haccou en Jessy de Cooker zijn beiden extreem te vroeg geboren.*

Medisch contact – Mei 2024

Dit artikel is tot stand gekomen met medewerking van volwassenen die te vroeg geboren zijn en hebben deelgenomen in de TINY-studie: Andrea Haccou, Anne Jongedijk-van Rossum, Jessy De Cooker, Juliëtte Kamphuis, Marcella van der Heijde, Mieke Verberkt, Amber Bontekoe, Parastou Hoseni, Katrien van de Stuijf, Christiaan Smit, Titia Struiving, Ingeborg Anna Martens.

Sylvia Obermann en Marijn Vermeulen hebben namens patiëntenvereniging Care4Neo het artikel kritisch meegelezen en voorzien van aanvullingen. Zij onderschrijven het pleidooi voor een persoonlijk behandelplan en de wens voor een expertisecentrum.

Het betoog wordt daarnaast ondersteund door ethicus Lien De Proost, gynaecoloog-perinatoloog Joanne Verweij en neonatoloog Rosa Geurtzen die ook dit artikel kritisch hebben meegelezen.

Cindy Cloin heeft de tekst kritisch meegelezen en geholpen met het structuur van het artikel en tekstuele aanpassingen

VROEGGEBORENEN WILLEN ZORG OP MAAT: 'LEVENSLANGE GEVOLGEN'

Volwassenen die als baby (veel) te vroeg geboren zijn, kampen vaak met psychische en lichamelijke problemen. Zorgverleners moeten zich hier meer van bewust worden, zodat klachten beter worden (h)erkend en eerder de juiste diagnose kan worden gesteld.

Jaarlijks wordt ongeveer zeven procent van alle baby's in Nederland te vroeg (<37 weken) geboren, waarvan 2500 tot 3000 baby's bij een zwangerschapsduur tussen de 24 en 32 weken.[1,2] De overlevingskansen van baby's die extreem prematuur geboren zijn, zijn de afgelopen decennia enorm verbeterd. Toch wordt ook steeds meer bekend over de langetermijneffecten die gelinkt worden aan vroeggeboorte. Denk daarbij aan chronische gezondheidsaandoeningen zoals een verhoogd cardiovasculair risicoprofiel, hypertensie en nierproblemen, of psychische effecten die later zichtbaar worden.[3,4,5]

Hoewel volwassenen die prematuur geboren zijn veel te danken hebben aan de medische zorg tijdens hun eerste, prille levensfase, plaatsen zij ook kanttekeningen bij de follow-up en nazorg. Dat blijkt uit de TINY-studie (*Towards INdividualized care for the Youngest*) van het LUMC, Radboudumc en Erasmus MC naar richtlijnen, besluitvorming en personaliseren van zorg rondom dreigende extreme vroeggeboorte. Zo vinden de volwassenen die deelnamen aan het onderzoek dat na de standaard follow-up van een aantal jaren, per individu beoordeeld moet worden of een langere follow-up nodig is en welke hulp er verder geïndiceerd is.

Voorgeschiedenis gaat verloren

Wanneer de kinderarts stopt met de follow-up bij vroeggeborenen – vaak gedurende de basisschoolleeftijd – is er meestal niemand meer met oog voor de gevolgen van de vroeggeboorte. Terwijl uit onderzoek blijkt dat het merendeel van de te vroeg geborenen vroeger of later te maken krijgt met gevolgen. Maar bij de meeste zorgverleners ontbreekt de kennis om voorkomende gezondheidsproblemen te linken aan de vroeggeboorte. In de zoektocht naar de oorzaak van bepaalde psychische of fysieke klachten, is dan ook opvallend vaak sprake van een gemiste of vertraagde diagnose bij deze groep. Als mensen zelf een verband leggen tussen hun klachten en de vroeggeboorte, blijkt het lastig om dit in de medische wereld bespreekbaar te maken. Zij krijgen dikwijls te horen dat het 'tussen de oren zit'.

De deelnemers aan de TINY-studie zouden daarom graag zien dat tijdens de anamnese door zorgverleners binnen de eerste-, tweede- en derdelijnszorg veel actiever hiernaar wordt gevraagd. Alleen zo kan er een verband worden gelegd tussen de vroeggeboorte en medische problemen later in het leven. Prematuriteit is immers een diagnose voor het leven.[6]

Voorbeelden

Eén van de deelnemers aan het onderzoek kreeg initieel een astmadiagnose, wat op latere leeftijd bronchopulmonale dysplasie (BPD) bleek te zijn. 'Sinds ik de juiste diagnose heb gekregen, gaat het beter met mijn longen dan ooit tevoren; ik krijg de juiste medicatie en onderzoeken.' Een ander deelnemer blijkt op 42-jarige leeftijd periventriculaire leukomalacie (PVL) te hebben, waarschijnlijk als gevolg van zuurstoftekort tijdens of kort na de bevalling. Ook blijkt na uitgebreider onderzoek dat één van de deelnemers hersenletsel heeft opgelopen, terwijl dit eerst werd geduid als ADHD met concentratieproblemen en gedragsproblematiek.

Op het psychische en cognitieve vlak wordt door deze groep volwassenen ervaren dat ze hun grenzen minder goed aanvoelen en regelmatig door hun lichamen teruggefloten worden. Een link tussen prematuriteit en psychische klachten is soms lastig te maken, maar ook een moeilijke start heeft veel impact op psychisch vlak: 'Niemand kon mijn klachten verklaren en ik was ten einde raad, ik zag het echt niet meer zitten', deelt iemand. De meerderheid van deze groep heeft moeite met het verwerken van gebeurtenissen of prikkels, vooral in stressvolle situaties: 'Ik raakte snel overprikkeld en kampte met woedeaanvallen. Vaak raakte informatie pas later de gewenste snaar – iets waar ik tegenwoordig soms ook last van heb, alsof zaken nog moeten verwerken in mijn brein.'

'One size doesn't fit all'

De huidige follow-up die nu landelijk wordt aangeboden is niet in iedere regio gelijk, en niet voor alle te vroeggeborenen toegankelijk. Alleen de kwetsbaarste groep (<30 weken zwangerschapsduur en/of <1000 gram geboortegewicht) heeft een indicatie voor follow-up. Sommige gezinnen ervaren problemen (tijd, geld, afstand) die hen belemmeren om naar het ziekenhuis te komen. Daarnaast bieden de ziekenhuizen niet allemaal hetzelfde, volledige programma aan. De standaardfollow-up duurt vijf jaar en in enkele ziekenhuizen, voor een selecte groep, tot acht jaar. Tot slot is de huidige follow-up voornamelijk gericht op de medische en fysieke aspecten, inclusief de cognitieve ontwikkeling, en minder op sociaal-emotioneel en gedragsmatig functioneren.

(H)erkenning

Het is in onze optiek noodzakelijk om de huidige follow-up te optimaliseren en naar een meer gepersonaliseerde aanpak te gaan. Hierbij is het belangrijk om te kijken naar de specifieke gezondheidsrisico's en problemen, de individuele behoeften en wat belangrijk is voor patiënt en familie. Het is niet zozeer relevant of de longfunctie of het IQ boven- of ondergemiddeld is, maar wat je hiermee kunt. Kun je naar een gewone school, kun je sporten, maak je vrienden (en relaties), kun je uit logeren, kun je thuis wonen, ben je zelfstandig/onafhankelijk, en hoe voel je je?

Naast (h)erkenning is het van belang dat er meer kennis komt door onderzoek te doen naar de relatie tussen vroeggeboorte en het medisch en psychosociaal functioneren op latere termijn.

Het opnemen van zwangerschap en geboorte in de voorgeschiedenis is een belangrijke eerste stap. Mede doordat het relatief zeldzaam is, weet niet iedere zorgverlener alles over mogelijke gevolgen en relaties tussen klachten en vroeggeboorte. Daarom zou een landelijk expertisecentrum voor zorgverleners, ouders en prematuren zelf wenselijk zijn. Experts uit verschillende disciplines, gespecialiseerd in de gevolgen van vroeggeboorte, zouden hier bereikbaar kunnen zijn voor vragen en overleg vanuit de kliniek, huisartsen of scholen. Dit alles kan bijdragen aan efficiëntere zorg, het eerder stellen van de juiste diagnose en een goed behandelplan.

Welke hulp is er al voor extreem te vroeg geborenen?

Op dit ogenblik kunnen kinderen en volwassen die te vroeg geboren zijn met hulpvragen over hun gezondheid o.a. terecht bij:

- Gestandaardiseerde, landelijke poliklinische follow-up vanuit het academisch ziekenhuis met de kinderarts-neonatoloog*;
- Poliklinische zorg in regionaal ziekenhuis door kinderarts, op indicatie;
- Consultatiebureau (GGD) gedurende de kinderleeftijd;
- TOP-programma (gespecialiseerd programma fysiotherapie voor extreem vroeggeboren kinderen);
- BPD-poli binnen het expertisecentrum Congenitale en perinatale longziekten van het Erasmus MC
- De cyberpoli voor late effecten van vroeggeboorte;
- Netwerk met ervaringsgenoten opgericht door neonatologie-patiëntenvereniging Care4Neo;
- Het Kleine Helden Huis, aanbod van zorg op maat voor kinderen die een moeilijke medische start hadden.

*indien <1000 gram geboortegewicht en/of < 30 weken zwangerschapsduur. Laatste follow up bij leeftijd 8 jaar

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Chapter 4

Voices of experience: what parents teach us about values and intuition in periviable decision-making

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Abstract

Objective: When extremely premature birth at the limits of viability is imminent, shared decision making with parents regarding the infant's treatment is widely recommended. Aligning decisions with parental values can be challenging. So, this study aims to get insight into (I) what values parents considered important in their decision, (II) whether their decision was based on intuition and/or rational analysis, and (III) parental suggestions on how to help explore and articulate values during prenatal counselling.

Design: A qualitative study was performed among Dutch parents who experienced (imminent) extremely premature birth. Diversity was aimed for through purposive sampling. Semi-structured interviews were conducted until saturation was achieved. Transcripts were coded and themes derived from the data.

Results: Nineteen interviews were performed. Results show what parents considered important in their decision, such as the infants' future, family life, and "giving a chance". Most parents made their decision more intuitively rather than rationally, for others both co-existed. Particularly fathers and parents who opted for palliative comfort care experienced the decision as rational. Parents would have liked to explore values, but found it challenging. They suggested strategies and conditions to help explore and articulate their values during counselling, such as a multidisciplinary approach.

Conclusions: Various considerations and underlying values were found to be important. Parents recognize the influence of emotions and intuition in decision-making and struggle to articulate their values, emphasizing the need for guidance. Healthcare providers should engage in open, personalized discussions to facilitate value exploration, enabling informed decisions aligned with parental values.

Background

Complex prenatal decisions arise when extremely premature birth is imminent between 22+0 and 26+0 weeks of gestation.[1] In this period, of which the exact application varies between countries and institutions, roughly two treatment options exist: early intensive care (EIC)-treatment or palliative comfort care (PCC).[2] Initiating EIC-treatment results in great prognostic uncertainty; some infants will not survive and others will survive with or without morbidities.[3] Since there is no 'best decision', most guidelines recommend a shared decision-making (SDM)-approach involving parental values.[4,5]

Within the context of SDM in case of extremely premature birth, value clarification (VC) can help in aligning a medical treatment decision with parental goals and circumstances.[6,7] It is essential to explore and incorporate the preferences and values of parents to guide their decision.[7] Studies have shown a variety of parental values playing a role in prenatal decision-making; values regarding quality of life (Qol), spirituality, religion, or the perception of the infant's suffering are examples of values that could be essential to parents.[8,9] However, some of these values (e.g. 'giving a chance') are multi-interpretable or require further exploration.[8] Additionally, parents commonly experience emotions such as anxiety and grief when extremely premature birth is imminent, which may affect their decision.[10-12]

Clarifying values appears to be challenging for healthcare providers (HCPs).[9,13,14] Understanding of values and the role of intuition in decision-making at the limit of viability is crucial for providing personalized counselling and further improving SDM.[15] This study aims to explore what parents considered important when faced with an imminent extremely premature birth, whether they relied on their intuition during this decision, and how they think VC should be performed. With these insights, counselling may be improved contributing to more value-congruent decisions.

Methods

Study setting and design

This qualitative research is part of the Dutch study called Toward INdividualized care for the Youngest (TINY), including qualitative research with extremely premature born adults (TINY-1) and experienced parents (TINY-2) to explore periviability guidelines, personalization, and parental values in the grey zone. In the Netherlands, the 24-to-26-week GA period is considered the grey zone allowing both EIC-treatment and PCC.[16] This article presents the TINY-2 results on parental values in prenatal decision-making. A more detailed description of the method with the COREQ-checklist is provided in *Appendix I*.

A Castor-database was developed including parents who either had experienced an imminent extremely premature birth <26 weeks GA but gave birth beyond 26 weeks, or if they were parents of an extremely prematurely born infant born between 24-26 weeks GA.

All parents in the database were invited to fill out a brief online questionnaire enabling purposive sampling to select a diverse group of participants (e.g., both PCC- and EIC-decisions, parents of survivors and non-survivors).

Based on literature and the research team's expertise, an interview guide was developed.[8] Two researchers conducted the interviews and were performed until thematic saturation was reached. Interviews were recorded, transcribed verbatim and analysed independently by two researchers (AB, LP) using thematic content analysis.

The codebook (*appendix II*) and analysis underwent several rounds of discussion and revision until all authors reached consensus. Results are presented in themes with subthemes, supported by illustrative quotations along with the corresponding interview number and treatment decision.

Results

Characteristics of participants

Nineteen out of 63 parents from the TINY-database were selected to participate. Semi-structured interviews were conducted between September 2022 and April 2023 with either the mother (n=12) or with two parents (n=7) (*Table 1*). The participants experienced imminent extremely premature births between 23+6 and 26+2 weeks GA. In four cases, PCC was chosen, while EIC was initiated in the remaining cases.

Results are represented in three sections corresponding with the interview questions.

Table 1 Demographic information

Characteristics of interviewed parents	
Place of interview	
Home	11
Hospital	2
Online	6
Interview with	
Mother	12
Mother and father	7
Total parents interviewed	26
Highest education of the interviewed parents	
Secondary school	1
Secondary vocational education	10
Higher professional education	10
University education	5
Religion	
No religion	20
Christian	6

Table 1 Continued

Characteristics of interviewed parents	
Experience with extreme premature birth between gestational age (GA) 24+0-26+0 weeks (n = 21)	
>1 extremely premature birth between GA 24+0-26+0	
Yes	2
No	17
Year of experience with extreme premature birth(s)	
2009-2013	6
2014-2018	8
2019-2023	7
GA at which extremely premature birth first threatened	
<23+0	2
23+0 – 23+5	5
24+0 – 24+6	8
25+0 – 25+6	4
>26+0 – <28+0	2
Birth between GA 24+0-26+0	
Yes	14
No, beyond 26+0	6
Other (extremely premature birth at GA 23+6)	1
Multiple birth	
Yes (twin)	7
No, singleton birth	14
Initial treatment decision between GA 24+0-26+0	
Intensive care treatment	17
Palliative comfort care	4
Outcome of the premature birth*	
Survivor(s) (incl gemelli)	10
Deceased	7
Both outcomes (twin)	4
Self-reported consequences of extremely premature birth	
None	
Any (retinopathy of prematurity, bronchopulmonary dysplasia, hearing loss, short bowel (Necrotizing Enterocolitis), complex sensory processing, social-emotional problems, language development problems, tube feeding, motor developmental delay)	10
	4

** The outcome of premature births is categorized as survivor, deceased, or both, accounting for both singleton and multiple births. For instance, the survivor(s) outcome encompasses singletons who survived or multiple births where both children survived.*

Parental considerations and values at the limit of viability

Several considerations and underlying values were described related to parental decision making. In general, parents struggled with the uncertainty of their infant's prognosis; "one moment you decide to go left, two days later you decide to go right" [19, PCC]. Themes that emerged were 'the future of the infant', 'family-life', 'everything done', 'to give a chance', 'trust', 'existing knowledge and experience', 'desire to have children, and 'hope'.

Future of the infant

An important theme was the infant's future, encompassing (I) statistics about chances, (II) the long-term consequences, and (III) long-term QoL.

Some parents expressed the importance of the statistics on survival and the chance of a potential disability. They questioned how far they were willing to go for their infant to survive. As for other parents, the role of statistics about future chances was very limited, because at that moment "that means nothing to you".

The infant's future QoL was also considered important by multiple parents, describing this as "enjoyment", "happiness", or the ability 'to be and act like others', such as "play sports", "have relationships" "eat by yourself", and "live independently".

Box 1: Quotes 'Future of the infant'

"What you actually want to hear is if [your child] is going to make it or not? And, what [disabilities] she will have?" - Interview 16 (Early intensive care treatment)

"*I imagined children in bed boxes and wheelchairs with tube feeding. And I thought: you would love them equally, but if you don't have to, you don't have to. She didn't have to survive at all costs"* - Interview 13 (Early intensive care treatment)

"*He doesn't need to be the best at school, but he needs a place in society*"

- Interview 14 (Early intensive care treatment)

Family life

The potential impact of an extremely premature birth on the family was also mentioned by parents. They thought about the implications for their own lives and their own happiness. In case of siblings in the family, they considered the impact of having an extremely premature infant on these siblings. As part of family life, practical factors like housing were discussed in terms of the possibility of adjustment to the house.

Box 2: Quotes 'Family life'

"There were two things that played a role: our child's happiness and our own happiness."

- Interview 7 (Early intensive care treatment)

"*[When we heard all the chances], we also thought: we have a two-and-a-half year old child. (...) I want my baby, but I also have a family"* - Interview 17 (Palliative comfort care)

Everything done

Multiple parents were inclined to do everything possible to fight, often more driven by emotions than by rational arguments. However, one couple changed their reaction from 'do everything' to PCC after learning about the statistics:

Box 3: Quotes 'Everything done'

"*We will do everything we can*" changed to "*If we were to reach week 25+3, we would want to consider administering the lung maturation injections.*" - Interview 1 (Palliative comfort care)

To give a chance

Some parents wanted to give their child a chance and 'go for it', meaning a chance to have a normal life or the chance to survive. Parents found it acceptable to give their infant a chance when they were assured there would be no unnecessary suffering, but they indicated they might reconsider this if the treatment became disproportionate.

Box 4: Quotes 'To give a chance'

"*I think that they really had a chance at a normal life, also because you heard about babies born at 25 weeks that did quite well. I would never forgive myself if I did not even try.*"

- Interview 3 (Early intensive care treatment)

"*[We wanted to give] a chance for survival. That ultimately, you can bring one or two girls home alive*" - Interview 4 (Early intensive care treatment)

Trust

Parents also based their decision on trust in the doctor and in science. One father felt uncertain as the birth approached, but his uncertainty dissipated upon the arrival of physicians with *"the expertise"*. Another couple mentioned they had trust in a good outcome.

Box 5: Quotes 'Existing knowledge

"*I work with children who have a disability, so I knew what could go wrong*"

- Interview 8 (Early intensive care treatment)

"We already had a lot of information from our firstborn. That makes things more concrete, you know what can happen, what trajectory you're entering and about the daily fears during your stay [at the NICU]. That made things easier for us." - Interview 17 (Palliative comfort care)

Existing knowledge and experience

Some participants already had knowledge about extremely prematurity and its consequences, since they worked in healthcare (n=7) or had prior experience (n=3). The information about consequences was more concrete to them, which could make decision-making more difficult for parents, but also easier.

Desire to have children

The intrinsic desire to have children was discussed as important in the decision. Among our participants, some parents did not conceive naturally, or the pregnancy was unexpected, because they thought to be infertile. This history played a role in both decisions to initiate EIC or to opt for PCC.

Box 6: Quotes 'Desire to have children'

"*Because we had a pretty tough time with the IVF process, (...) it was a real rollercoaster. And once you've come so far, we just felt like we wanted to take the chance even though that chance is so incredibly small*" - Interview 11 (Early intensive care treatment)

"*We got pregnant through IVF. So, for the second pregnancy, we thought about how far we wanted to go, knowing the risk of premature birth. (...) Nobody can guarantee you that everything is going to be okay*" - Interview 17 (Palliative comfort care)

Hope

Lastly, hope that it would go well for their infant was mentioned by some parents. One father described it to be natural to draw hope from everything and to keep searching for some certainty that it would turn out well for your infant.

Intuition and rational

The majority of the parents experienced their decision-making as intuitive with a lot of feelings involved; "*You can provide statistics and chances, but I think most parents make the decision based on their feeling"[4, EIC].* Some parents experienced the decision as a combination of rational and intuition. They had some time to reflect on the information and balance their feelings and values. However, participants acknowledged that feelings and intuition might take over when there is no time to decide: "*You had to decide very quickly, so you could not turn your feelings off"[7, EIC].* Mainly the fathers indicated that they experienced the decision as rationally made: "*It was a risk, but a calculated risk"[7, EIC],* or mothers indicated that their partners approached the decision more rationally: "*I'm actually quite a sensitive person myself. My husband is a bit more rational"[18, PCC]*. Furthermore, parents who opted for PCC often expressed their decision as rational. Participants mentioned that it is essential for HCPs to look at individual's needs; to explicitly clarify values or listen to intuition and feelings.

Value clarification experiences

VC may help in aligning decisions with values that are important to parents. However, many participants could not recall whether they discussed their values and considerations during counselling with the physician: *"Perhaps [having no memories of those moments is] simply because you were truly overwhelmed."[10, EIC].* Although parents would have liked to discuss their values and considerations during counselling, they felt it would not have changed their decision as they believed they had all the necessary information. However, it may provide them with a sense of making a more informed and carefully considered decision.

To help parents formulate and discuss their values, they suggested to have a conversation with questions like: '*Let's see what you find important in life, or what you want for you child"[1, PCC]*, and help them with their values: *"Ask the parents a couple of questions which will give parents an idea of values to consider/think about"[5, EIC]*. Parents expressed concerns that this should not feel like '*an interview*' or '*the need to defend yourself*''. A more multidisciplinary approach was most frequently suggested. They suggested to include nurses,

psychologists, or social workers because parents thought physicians were not necessarily trained to talk about values. Support should be offered for making a decision, without aiming in a certain direction. In *Table 2*, all strategies suggested by parents are recorded.

Table 2 What parents teach us about how to help them to explore and formulate values

Suggested strategies to explore and formulate values
Personalization: Personalize, address parents' needs, adapt the conversation to those needs. Take into account that there will be parents who do not feel the need to discuss their values or what they consider important in the decision at the limit of viability. *"How can I help you to make this decision?"*
Examine: Assess whether parents understood everything about what will happen and what is ahead of them when their child is born extremely premature.
Questions: Ask parents questions after an introduction with information about considering values in this decision. Examples mentioned: "*What are values that you consider important in life?"* "*What do you consider important in life?"* "*What do you consider important for your child?"*
Examples: Discuss examples of values that parents could consider in their decision at the limit of viability.
Decision aid: A decision aid designed to explore values or preferences for their infant's future should be designed and/or incorporated into existing decision aids. It should contain questions and examples to assist parents in exploring and articulating their values.
Potential later decision moments: Inform parents that additional decision-moments may follow later. Explain to parents that in case of future complications, intensive care treatment may not be in the best interest of their child anymore, and treatment can be withdrawn.
Prepare during (high risk) pregnancy: Preparation during regular checks by the midwife/ gynecologist, especially for the group of pregnant persons with a high-risk pregnancy. Not in an overwhelming manner, but for example with a brochure. So, if you prefer not to read about the possibility of extremely premature birth and the decision at the limit of viability, that would be an option. The choice would be up to the person.
Suggested conditions to facilitate the exploration and formulation of values
Communication/give unbiased information · Create the environment for an open and honest conversation · Take parents seriously · Information provision in a friendly manner · Information provision in clear, understandable language
Decision-making · Ensure that the pregnant person is with another person to hear all the information · Give the parent(s) some time to think about it, adjusted to each individual situation · If possible, a second or third counselling's session
Make it multidisciplinary with the right professionals · The presence of a NICU-nurse · The presence of a psychologist · The presence of a social worker

Discussion

This study aimed to explore parental values during treatment decisions at the limit of viability, the role of intuition, and suggestions to help parents formulate values. Several notable findings emerged from our results.

Considerations and values of included parents mostly revolved around the infants' future and the impact on their family, consistent with prior studies.[17,18] Unlike international literature, religion and spirituality were not mentioned by our participants, potentially reflecting differing cultural values.[19] A recent review about common values considered important at the limit of viability showed the complexity and multi-layered nature of values. Some values reflect on process preferences, such as the desire to do everything possible, while other values reflect on feelings or intuitions.[8] Our findings demonstrate that probing parents about their considerations could specify the meaning of underlying values and their impact on decisions. For example, by exploring various personal interpretations of QoL, we uncovered what parents aspired for their child's QoL, and how this can shape their decision. Additionally, values should be explored without assumptions or biases. Among our participants, the desire to have children supported both EIC- and PCC-decisions. This emphasizes the variability in how a certain value can lead to different decisions, highlighting the importance of avoiding assumptions about an eventual decision. HCPs should explore parental values further to understand and align parental values into value-congruent decisions.

Participants acknowledged both the intuitive and rational aspects of decision making, with more emphasis on intuition and gut-feeling. This emphasis was even more pronounced when time was limited. However, particularly fathers and parents who opted for PCC emphasized the rational aspect of the decision-making process. Existing literature discusses that individuals can differ in their approach to decision-making, with some leaning towards a rational approach, analysing data and considering pros and cons, while others embrace an intuitive decision-making style, relying on gut feelings and instincts.[20] Intuitive and rational decisions at the limit of viability have not been described explicitly yet. Some research suggests that decisions are best made through analytical reasoning, and feelings interfere with good, rational decision-making.[21] Other research suggests that intuition may be surprisingly accurate by integrating existing values into decisions, because it can be based on an implicit integration of a large amount of information and may play a pivotal role in shaping preferences.[21,22] Our participants perceived their decision to opt for PCC as rational, a perception that may imply a sense of counter intuitiveness associated with palliative care decisions, because it goes against what parents instinctively want: a living child. Our results further underscore that intuition and rationality can co-exist or even be intertwined and dependent on each other. Rationality can be used to gather and analyse information, while intuition helps with judgement and interpretation of this information.[23] Yet, gently challenging the initial preference to check whether it is stable or not, may improve how parents feel about the decision in the long run.[14]

Lastly, our study offers beneficial suggestions to help explore values during prenatal decision making. By exploring values, a treatment decision can be aligned with personal goals and circumstances.[23] Despite its acknowledged importance, several studies show this is not always practiced.[13] Our results underscore this trend, with parents expressing a lack of recall regarding discussing their values during counselling. Generally, parents in this study acknowledged both the importance and challenges associated with exploring their values, expressing the wish for an active role for themselves in this process. They emphasized the need for HCPs to assist in articulating and constructing values for making decisions congruent with their values, as other experts suggested.[24,25] Although participants stressed the importance of an unbiased neutral approach, achieving this is challenging. Formulating values and preferences can be influenced by parents' and HCPs' prior knowledge, bias, and emotions.[24,26,27] HCPs might, inadvertently, influence the process by framing information due to their own values or bias.[24,28] Therefore, addressing those challenges is essential.

Some of the participants' suggestions align with literature about VC-strategies, including unbiased information, building a trustful patient-counsellor relationship, allowing extra time for parents to let them absorb information, and promoting participation by empowering parents.[28-31] Newly suggested practical recommendations how to initiate the conversation and conditions to facilitate the exploration of values are provided, such as adopting a multidisciplinary approach or preparing parents during pregnancy. Furthermore, literature suggests talking to a significant other or utilizing value-clarification exercices.[7,32] Not all parents may perceive the necessity of clarifying values in general, choosing not to engage in this process or do this independently. Therefore, HCPs should explore preferences in formulating values during SDM.

Strengths and limitations

This study has several strengths offering a unique perspective of experienced parents on the SDM-process and explores beyond the existing literature in this topic area. Purposive sampling was used to select a diverse group of participants ensuring variations in experience with extremely premature birth and personal backgrounds. We achieved a broad selection of participants, increasing the external validity. Furthermore, the interdisciplinary nature of the research team contributes to the study's strength.

This study also has limitations. First, some findings of this study may be specific to the Dutch context and its societal values, which may limit their generalizability to other countries or healthcare systems. However, the overarching principles, such as the complexity of values, the need for probing deeper with follow-up questions and the role of intuition, derived from the study can still provide valuable guidance in diverse cultural contexts. Secondly, despite our efforts with purposive sampling, we faced challenges in recruiting parents with various religious and cultural backgrounds, members of the LGBTQIA+-community and parents who opted for PCC. However, a described Dutch cohort shows the decision for PCC occurs much less frequently than active care (8% vs. 92%).[33] Third, the

results may be limited by recall bias worsened by the emotionally overwhelming situation that parents faced at that time.

Conclusion

Parents experienced a significant role of overwhelming emotions and a gut-feeling in their decision, yet they acknowledge the importance of discussing values during counselling. However, exploring and formulating these values is challenging for them, underscoring the need for assistance. Improving skills to help parents formulate their values and create conditions facilitating this process could lead to better understanding parental values.

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Appendix I: detailed description methods

Study setting and design

The current Dutch guideline on care for extremely premature infants born <26 weeks gestational age (GA) dates from 2010.[1] In the Netherlands, the 24-to-26-week GA period is considered the gray zone allowing both EIC-treatment and PCC.[2] We performed a qualitative interview study among Dutch parents who experienced an imminent or actual extremely premature birth in this gray zone post-2010. Ethical approval was obtained from the Medical Ethics Committee Leiden-Den Haag-Delft, the Netherlands, in November 2021.

TINY-study

This research is part of the Dutch study called Toward INdividualized care for the Youngest (TINY), initiated from three perinatal centers in the Netherlands: Erasmus MC Rotterdam, LUMC Leiden, and Radboudumc Nijmegen. As part of the TINY-studies, we conducted qualitative research with extremely premature born adults (TINY-1)[3,4] and with experienced parents (TINY-2) to explore periviability guidelines, personalization, and parental values. This article presents the TINY-2 results on parental values in prenatal decision-making.

A Castor-database was developed for this study. Parents were included if they had either experienced an imminent extremely premature birth <26 weeks GA but gave birth beyond 26 weeks, or if they were parents of an extremely prematurely born infant.

Parents were approached through the Dutch patient organization Care4Neo for parents who have a baby that need to be placed in an incubator and the infant itself, the Dutch platform Stille Levens - kenniscentrum Babysterfte for parents who supports bereaved parents and others who are affected by the death of a baby, physicians' networks of patients, social media platforms, e.g. Instagram and Linkedin of the NICU-departments of the involved hospitals and researchers, or through parents of previous studies (PreCo study[5], CODA-study) who gave permission to be contacted again.

Participant selection

All parents were invited to fill out a brief online questionnaire, providing essential demographic details about themselves and their experience with extremely premature birth. This information was used to select parents from the database by purposive sampling to include a diverse group of participants for this research (e.g., both PCC- and EIC-decisions, both parents of survivors and non-survivors). Our aim was to include a group of parents with a wide variety in educational level, age, geographic regions within the Netherlands and different experiences with extremely premature birth based on the gestational age of the imminent extreme premature birth, the actual birth in the gray zone or not, the year of the extreme premature birth, the number of extremely premature births, the decision made at the limit of viability, the infant's survival or the potential longterm consequences of the infant.

Data collection

Based on literature and the research team's expertise (neonatologists, maternal-fetal-medicine specialist, psychologist, and ethicist), an interview guide was developed.[6] The interviews were conducted in the participants' homes, the hospital, or online using Microsoft Teams, based on the participant's preferences. A medical doctor (AB) and bioethicist (LP) conducted the interviews and were performed until saturation. Informed consent was obtained from all participants. Interviews were recorded and transcribed verbatim.

Data analysis

Two researchers (AB, LP) independently analyzed and coded the interviews using a thematic content analysis approach.[7] The codebook and analysis underwent several rounds of discussion and revision until all authors reached consensus. The manuscript followed the COnsolidated criteria for REporting Qualitative research (COREQ)-checklist to report methods and results.[8] In the results section, themes with subthemes are presented, supported by illustrative quotations in boxes and in the manuscript along with the corresponding interview number and treatment decision (EIC = early intensive care treatment, PCC = palliative comfort care).

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Appendix II: codebook

Theme / codes eng (nl)	Definition
Everything done 'Do everything' (er alles aan doen)	Parents wanted to "do everything" in the decision at the limit of viability
Give a chance 'Go for it' (ervoor gaan) 'Giving a chance' (een kans geven) // 'Try' (proberen) · A chance to have a life · A chance to survive	Parents wanted to go for it when their infant was born at the limit of viability Parents wanted to give their infant a chance when their child was born. On the question what chance they wanted to give their child, the following was answered: · They wanted to give their infant a chance to have a life · They wanted to give their infant a chance to survive
Hope 'Hope' (hoop) ● Hope that it will be okay	When making a decision at the limit of viability, hope played an important role in their decision. Parents said they had hope it would be okay in the end
Uncertainty in the decision 'Uncertainty' (onzekerheid)	Parents mentioned the uncertainty regarding the outcomes/prognosis in the decision
Trust 'Trust' (vertrouwen) · In the doctor/science · In a good outcome	Parents mentioned they based their decision on trust.. · .. in the doctor · .. in a good outcome
Existing knowledge and experience 'Background knowledge' (achtergrondkennis) · From work in healthcare · From earlier experience with premature birth	One of the parents or both parents had already (some) knowledge about extremely premature birth, and this played a role in their decision-making process. · Parent(s) had more knowledge because they work in healthcare · Parent(s) had more knowledge because they experienced an extremely premature birth before.

Theme / codes eng (nl)	Definition
Future of the infant 'The chances for the child' (de kansen voor het kind) · Chances of survivial · Chances of a disability · At that moment chances mean nothing to you · Quality of life for the child' (kwaliteit van leven kind) · How happy can you be? · Living life, to be able to.. ..go on vacation ..play a sport ..have relationships ..run, swim, play ..be a child, to nurse, to crawl, to discover the world ..communicate, to live or share life with each other ..eat by yourself, live independently, be self-reliant ..participate in society 'Long-term outcomes for the child' (lange termijn gevolgen kind) · Handicaps	The chances for the child, told during counselling, were important for parents in making the decision regarding treatment after birth. · Parents mentioned specifically the chances of survival for their child · Parents mentioned specifically the chances of a disability for their child · During counselling the chances for the child were told, but at that moment it did not mean anything for the parents · Parents found quality of life for their child very important in their decision-making · In term of quality of life, parents questioned if you could be genuinely happy when their child had a chance to be limited in their functioning · When asked what quality of life meant for parents, they came with various examples what they wanted for their child. Parents considered the long-term outcomes for the child during their decision at the limit of viability. · Parents described the long-term outcomes in terms of potential handicaps.
Family-life 'Family' (gezin) 'Social factors (e.g., housing, financially, etc) (Sociale factor (vb. Huis, financieel, etc)) · Practical reasons · Maternal age 'Future suffering for the parents' (Toekomstig lijden van ouders)	Parents considered the burden/consequences of an extremely premature birth and infants on the rest of their family. Parents considered the burden/consequences of an extremely premature birth and infants on other social factors than their family. Parents considered the more practical reasons during the decision. Parents took into account the maternal age for their decision. · Parents considered their own potential suffering of having an extremely premature infant, that potentially could have an handicap
Desire to have children 'Wish to have a child' (kinderwens) 'IVF' (IVF)	The wish to have a child and the effort it took to get pregnant played a role in the parental decision at the limit of viability When parents mentioned IVF to get pregnant and as consideration in the decision.

Intuïtion vs. ratio

Theme / codes eng (nl)	Definition
Intuition vs. ratio · **Ratio** · **Intuition** · **Both**	When the question above was asked, parents answered with the following Parents found a the decision a rational decision Parents based their decision on feelings and intuition Parents made the decision based on both feelings and intuition and rational thinking about what was important to them.
Is that okay?	Do parents think that making the decision at the limit of viability based on feelings and intuition is okay?

Value clarification

Theme / codes eng (nl)	Definition
Value clarification during counselling · Did not · Did	Parents did not discuss their considerations with their physicians during counselling, but only received information about the chances for their child. Parents discussed their considerations with their physicians during counselling, after receiving information about the chances for their child.
Ways to clarify values **How to clarify values?** · Ask the question · Help with what sort of values are important to consider/asd question about those values **'VC multidisciplinary'** · Nurse · Psychology/MMW ***How not to clarify values?*** ● Defending their decision Not necessary at that moment	Parents discussed ways how to and how not to clarify values during counselling about the treatment of their infant at the limit of viability Parents discussed ways how they think physicians should clarify values during counselling Ask the question: what is important in your life and discuss this further with parents The HCP should help parents with what sort of values they can consider for this decision. The counselling should involve other disciplinaries. A nurse should be included in prenatal counselling A psychologist or social work should be included in prenatal counselling Parents discussed that when you explore parental values during counselling, the parents should not feel like they have to defend their decision

Part II

The artificial amnion and placenta technology as potential treatment for extremely premature infants

Chapter 5

Navigating the ethical landscape of the artificial placenta: a systematic review

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Prenatal diagnosis, 2025

Abstract

This systematic review aims at presenting the ethical debate on the artificial placenta (AP) by identifying, distinguishing, and organizing the different ethical arguments described in the literature. Articles were selected based on predefined inclusion criteria: discussing ethical arguments, on AP, written in English. QUAGOL methodology was used for analysis. Forty-five articles were included. We identified three themes. First, foundational-ethical issues. There is disagreement on whether the AP subject should be considered an infant or a new moral entity. While physiologically it stays a foetus, it sits outside the womb. Second, reproductive ethics issues. Few authors believed that the AP would increase reproductive choices. The majority warned that the AP could limit reproductive choices by creating pressure to use it in healthy pregnancies or as an alternative to abortion. Third, research ethics issues. Publications mostly focused on selection of the in-human trial participants. We concluded that AP ethical literature focuses mostly on the potential use of AP as an alternative to abortion or healthy pregnancies rather than on the intended use as treatment after extremely premature birth. We conclude, therefore, that the current ethical literature on AP is imbalanced: it leans more towards science fiction than actual clinical and technological reality.

Introduction

The artificial placenta (AP)[1] is being developed to improve survival and quality of life of extremely premature infants (EPIs) between 22 and 28 weeks of gestation. Currently, EPIs experience high mortality and morbidity,[1,2] with the latter being partially iatrogenic.[1,3,4] By mimicking the function of the placenta, the AP aims to preserve a physiological fetal state, and therefore prevent severe complications of extreme prematurity.[5]

Reflecting on the AP's ethical implications before implementation is necessary to integrate ethical reflection in the technology development. The ethical debate on AP is complex. It involves different stakeholders (e.g. parents, developers, clinicians, ethicists), each with their own perspectives.[6] Further, AP raises many ethical questions beyond treatment of EPIs.[7] For example, should it be offered as an alternative to abortion? Hence, we conducted a systematic argument-based review[8,9] to identify, distinguish, and organize the different ethical questions and arguments described in the AP literature. This could help experts to better understand the current debate and identify potentially overlooked issues. This, in turn, contributes to further inclusion of ethical considerations in the further development and implementation of the AP.[6]

Methods

A systematic search of Medline®, Embase®, Web of Science™, and Scopus® electronic databases was conducted on November 17th 2022, and updated on November 13th 2023. The complete search strings are reported in *Appendix 1*. A librarian from the Leiden University Medical Centre assisted with the development of the search strings. We used the "snowball method" and citation tracking on every included article to identify additional relevant publications.[10]

Eligible articles were selected based on predefined inclusion/exclusion criteria (*Table 1*). We are aware that a plethora of different terms are used to identify artificial placentas or partial ectogenesis. To ensure consistency, we only included articles discussing technologies able to maintain part of the gestation outside the human womb, regardless of the term used for the technology or the process. Further, to ensure scientific rigor, we excluded articles that did not define the technology discussed or whose definition was too ambiguous to determine what technology was being discussed. Two authors (AC and ADB) independently screened titles, abstracts, and full texts. Disagreements were resolved by discussion with a third author (LDP) until consensus was reached. A PRISMA flow diagram[11] summarizes the literature search process (*Figure 1*).

1 Authors use different terms to identify this type of technology depending on whether they are referring to a specific prototype (e.g. biobag or EVE), an aspect of the technology (e.g. artificial amnion and placenta technology), or its general aim (e.g. artificial womb technology). We use the term artificial placenta as it encompasses all the different specific prototypes while differentiating it from artificial wombs able of maintaining an entire pregnancy outside the human womb.

Table 1 Inclusion and exclusion criteria for selection of articles

	Included	Excluded
Types of publication	· Published articles.	· Dissertations, books, book chapters, guidelines, ethics policies and codes, because these publications cannot be systematically searched, which will affect the reproducibility.
Topic	· Publications focusing on the artificial placenta as a technology that mimics the placenta and amniotic sac, and that partially maintain the foetus outside the human womb. · Publications focusing on artificial placenta specifically for infants born at 22-25 weeks of gestation (domain 3 in De Bie et al. 2023). · Publications focusing on partial ectogenesis. · Publications containing original ethical arguments. Articles that use existing concepts and theories to develop an original normative stance, or a new theory or concept are included. Similarly, articles that develop new concepts or theories to support an existing position are included.	· Publications on artificial wombs as a technology able to maintain the whole gestation outside the human womb. · Publications focusing on full ectogenesis; e.g. Smajdor 2007.[68] · Publications that do not clarify whether they refer to artificial placentas or artificial wombs as previously defined; e.g. Räsänen 2017.[69] These two technologies are different and different ethical arguments might apply. Our aim is to review arguments related to the artificial placenta technology specifically. Including articles that do not specify what technology they are referring to will introduce vagueness and bias. · Publication focusing on IVF as partial ectogenesis. · Publications describing clinical trials or the technical functioning of the artificial placenta without ethical reflection. · Publications describing what legal provisions would regulate AP, how, and how these provisions would change without ethical reflection on these changes and/or without taking a position on which changes are advisable. · Reviews that present a mere overview of existing ethical arguments without elaborating a normative stance, because (1) no new original content is presented, and (2) reviewed articles are already included with the risk of duplicating results and over emphasising certain positions.
Language	· Publication language is English.	· Non-English language publications.
Date	· Screening of articles was not limited by publication date; entire date range was included in searches of Medline®, Embase™, Web of Science™, Scopus® databases.	· NA

We relied on the journals' peer review process to assume that the quality of included articles was sufficient. This is acceptable as the aim of our review is descriptive not normative. [12]

Data analysis and synthesis followed the Qualitative Analysis Guide of Leuven (*Table 2*). [13,14] The analysis was conducted in an interdisciplinary research team comprising expertise in medicine (EJV, ADB), and bioethics (AC, LDP, CG).

Table 2 Data analysis and synthesis

Step[a]	Description
1. Familiarization with the publications	We repeatedly read the articles to familiarize ourselves with the material.
2. Development of individual conceptual schemes	For each article, AC developed an individual conceptual scheme summarizing the concepts and arguments emerging from the included articles. The schemes were refined based on team discussion.
3. Development of overall conceptual scheme	The individual conceptual schemes were compared to identify recurring concepts and arguments as well as relevant differences and nuances. AC merged these elements into a single overall conceptual scheme and refined the scheme after team discussion.
4. Reporting of results	We reported the results based on the overall conceptual scheme.

[a]*An interactive relationship between publications, individual schemes, and overall scheme was maintained during the whole process to avoid overlooking relevant nuances and to ensure that we preserved the original meaning of the included publications.*

Results

We identified forty-five eligible publications, whose characteristics are described in *Table 3*. Most publications were published from 2020 and originated mainly from UK, North America, and Australia. Many articles were written by the same first author. Most authors are scholars in philosophy, bioethics, or health law.

Table 3 Characteristics of included publications (N=45)

CHARACTERISTICS	# OF PUBLICATIONS
Article type	
Full article	26
Commentary	19
Year of publication	
2020-2023	38
2015-2019	7
First author's number of included publications	
Romanis E.C.	6
Colgrove N.	3
Horn C.	3
Kendal E.S.	2
Kingma E.	2
Mercurio M.R.	2
Simkulet W.	2
Verweij E.J.	2
Werner K.M.	2
Cohen G.I, Kennedy S., Nelson A., Overall C., Rodger D., Segers S., Stratman C.M, Wozniak P.S., De Proost L., Krom A., Cordeiro J.J., De Bie F.R., Esquerda M., Hine K., Holmes J., Kimberly L.L., Roesner N., Takashima K., Muhsin S.M., Kukora S.	1 (each)
Country of first author's affiliation	
USA	20
UK	14
The Netherlands	4
Australia	2
Canada, Belgium, Spain, Japan, Singapore	1 (each country)
First author's professional background[1,2]	
Philosophy, bioethics	14
Healthcare	6
Law	6
Not found	3

[1]*To determine the first author background we looked at the professional titles indicated in the papers and at the professional biography in the indicated institution website.*
[2]*Authors with multiple publications were only counted once.*

We identified three main themes: foundational-ethical issues; reproductive ethics issues; and research-ethics issues (*Figure 2*).

Foundational-ethical issues: The moral status of the AP subject

Several terms were coined to identify the AP subject, e.g. gestateling, fetonate or perinate. [15] Further, disagreements exists on the moral status of the AP subject. Some stated that the AP subject is "a foetus (physiologically) that we treat as a neonate (morally)",[15] but the main discussion is on whether the AP subject is a new moral entity or an infant.[16-19]

The AP subject is a new moral entity

Some authors claimed that the AP subject is a new moral entity.[20-27] Hence, concepts and rules that apply to foetuses or infants do not apply to AP subjects, who require ad-hoc protections. [20,21,23-27] These authors conceptualize the AP subject as a new moral entity for several reasons.

First, some authors claimed that AP subjects are not physiologically born.[20,21,23-25] They explained that birth implies a change of location from the womb to the external environment *and* a change of physiology, e.g. the lungs inflate. The AP subject is only geographically born because it did not change physiology. [20,23-25]

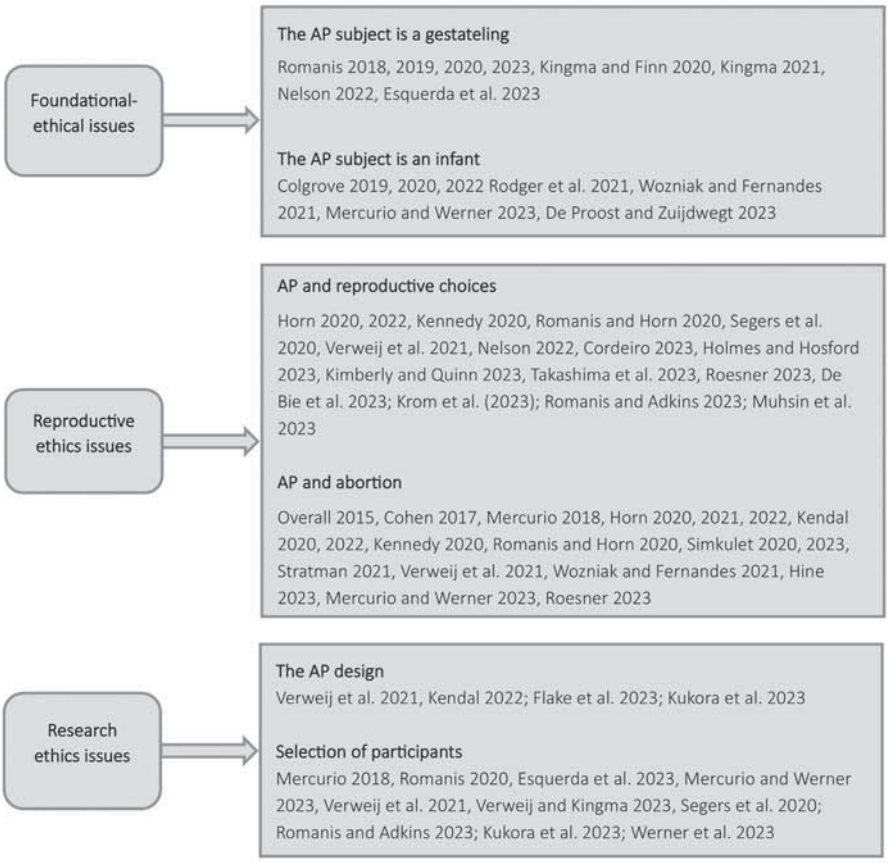

Figure 2 Distribution of included publications based on the identified themes and sub-themes.

Second, according to Romanis, AP subjects, which she has termed "gestatelings", have no capacity to live independently.[23-25] Romanis explained that the physiological change grants infants independent capacity for life, whereas AP subjects did not physiologically change and, consequently, are still completely dependent on the AP. [23-25]

Third, according to Romanis, while the preterm infant has direct contact with the parents and the external environment, the AP subject is completely isolated from the external environment. For Romanis, "this isolation will influence the perception of and, on occasion, the feeling attached to each entity".[23;] Implying, in this way, that AP subjects will be perceived and treated differently than infants.[23-25]

The AP subject is an infant

Others claimed that the AP subject is an infant[15-18,28-30] for several reasons.
First, they believe that the AP subject is born because, [16-18,28,29] based on the conventional definition of birth, "being born" means being completely expelled from the womb, and showing evidence of life, such as breathing or having a heartbeat.[16-18,28] The AP subject is completely expelled from the womb and shows evidence of life as it has a heartbeat, thus it is born.

Second, they maintained that the AP subject has some capacity to live independently.[29] For example, the subject must be sufficiently developed to survive the surgery required for the transfer in the AP. Further, Colgrove elicited that the conventional definition of birth does not require independency as it refers to evidence for life "however supported".[16,17] Finally, Wozniak & Fernandez reminded that no infant has independent capacity for life because they all need care to survive, and, therefore, this is not a distinctive characteristic of AP subjects. [29]

Third, they argued that EPIs are also more similar to foetuses than infants, but parents and clinicians treat them as children.[15,30] Two publications conceded that Romanis' term gestateling could identify an infant treated with AP, but this does not imply that the AP subject is not an infant in the same way in which EPIs are specific infants born prematurely, but they are infants nonetheless.[16,30] Conversely, Mercurio warned that introducing a new term could suggest that AP subjects are not given the same level of care and compassion as other infants.[30] Therefore, these authors believed that AP subjects have the same rights and protections of infants.[16-18,28]

Reproductive ethics issues: Impact on reproductive choices

Krom et al. proposed to use the capabilities approach to obtain a comprehensive and nuanced understanding of how AP will affect the pregnant person and the infant.[31] For example, a risk of prematurity is survival with severe disability, meaning that AP needs to be incorporated in a broader system of healthcare to ensure long-term support.[31] Two specific

reproductive ethics issues were identified: how AP will affect reproductive choices, and how it will affect abortion rights in particular.

AP and reproductive choices

A first question in the literature is whether AP will increase or decrease reproductive choices. Kennedy elicited that AP might increase reproductive autonomy by increasing reproductive choices, e.g. choosing AP as an alternative to abortion. To the opposite, seven publications warned that AP might reduce reproductive autonomy.[32-38] Three publications explained that AP might increase social pressure to use it for the foetus' benefit.[36-38] Five publications warned that access to AP might be limited to traditional family units, as it already happens in some countries for IVF, or it might be too expensive.[32-36] Therefore, AP implementation should be preceded by structural interventions to prevent inequalities.[32-36]

A second question is whether pregnant people should be allowed to choose AP as an alternative delivery option even when not medically indicated. Nelson maintained that whether to choose AP is a reproductive choice. As such, access to AP should not be limited because this would be an infringement of autonomy, which could generate anxiety, distress, and delivery-related post-traumatic stress disorder.[22] Holmes and Hosford concluded that AP might be acceptable for non-medical reasons, e.g. to pursue career or education, as these will benefit the pregnant person, the child, and society.[39] To the opposite, two publications maintained that the AP medical risks are too high to justify it when non-medically indicated.[40,41] In analyzing AP acceptability based on Islamic legal maxims, Muhsin et al. concluded that using AP when not medically indicated – specifically to avoid the burdens of pregnancy, for single fathers or gay couples, and for abortion - is not consistent with Islamic precepts.[42]

A third question is whether a pregnant person should be allowed to refuse AP if medically indicated. Two publications concluded that pregnant persons should not be obliged to choose AP,[43,44] although Takashima et al. believed that they could be subjected to some sort of mild punishment like blame.[43]

AP and abortion

There are two main points discussed: if and how the AP will affect abortion rights; and whether it should be an alternative to abortion.

Will the AP affect abortion rights?

Six publications claimed that AP might lower the viability threshold, i.e. the week at which a foetus is considered capable to support life.[30,34,38,45-48] Depending on how we reinterpret viability, it might reduce or expand abortion rights because several laws use viability thresholds to determine when abortion is permissible. Cohen theorized that, if AP will lower the viability threshold, jurisdictions that only allow abortion up to viability could lower the abortion threshold. However, countries that prohibit abortion could allow AP instead of a total ban on abortion.[45] Kendal answered that viability is not an intrinsic characteristic of

the foetus, but it depends on external factors (e.g. resources available in the hospital), and indeed, it varies greatly worldwide. As AP is not the only technology challenging viability, it must not affect abortion laws.[48]

Should AP be an alternative to abortion?

Two authors explained that historically the abortion debate focused on whether there is a right to terminate the pregnancy, regardless of whether the foetus could survive, as survival was impossible. As AP will allow to terminate a pregnancy without terminating the foetus, they elicited that the abortion debate is now focusing on whether AP should be a compulsory alternative to abortion.[45,49]

Simkulet and Stratman claimed that, assuming that AP is safe and not riskier than abortion, AP should substitute abortion because it allows a cessation of pregnancy without killing the foetus.[49,50] Stratman bases this statement on two assumptions. First, parents do not own a child or a foetus, so they do not have right to its destruction, and even if they do own it, this does not make its destruction moral. Second, the harms of having a biologically related human against their will are not grave enough to warrant the death of the foetus.

To the opposite, others claimed that AP is *not* an alternative to abortion, and that considering it as such is ethically problematic.[33,34,46,48,51-54] On a practical level, they said, most abortions occur in the first trimester and are minimally invasive, whereas AP can only be effective from 22/23 weeks and requires a C-section.[33,34] Enforcing AP instead of abortion means obliging pregnant people to stay pregnant longer than they want, and to undergo an invasive surgery instead of the safer and less invasive option, and to become biological parents against their wish, which is an infringement of bodily autonomy.[33,36,48,52,54] Two publications added that substituting abortion with AP will increase the infants in the adoption system.[52,53] Further, conceptually these authors reject that abortion is a moral issue to be solved.[32-34,46,48] They explained that abortion is a basic form of reproductive care and, as such, abortion and AP can coexist: a pregnant person should be allowed to decide whether to continue the pregnancy, have an abortion, or choose AP. Finally, Horn warned that, as AP will likely be an expensive technology, making it compulsory will penalize poorer people, because they might be punished for not using a technology they cannot afford.[32,33] She explained that this is not farfetched as in the US women can already be punished for behaviors that place the foetus at risk.[32,33]

Research-ethics issues: Development and trial

Mercurio and Romanis stated that the safety and efficacy of AP should be assessed through clinically and ethically solid trials that prioritize participants' safety.[25,41,47] Two publications explained that different AP prototypes work differently.[55,56] Hence, while some ethical considerations apply to all prototypes, e.g. the importance of minimizing risks, other are prototype-dependent, e.g. considering the C-section risks because not all prototypes require a C-section. Therefore, the risks of each prototype should be assessed individually.[56]

Two main aspects of the development and trial are considered: The AP design, and the selection of participants.

The AP design

Included publications explained that it is important to consider the AP design as its aesthetic can contribute to how it is perceived and used.[38,51] For example, Kendal explained that much of the distrust toward AP can be explained by the fact that we already have a long history of sci-fi imaginary (e.g. The Matrix) that included artificial wombs sustaining entire gestations in pods as a crucial negative element of their dystopias. People tend to associate the two, which lead to negative attitudes toward AP.[57] Because of that, Verweij et al. emphasized the importance of involving parents and caregivers in the design process and to consider their input on design choices. For example, if we know that parents prefer to always see their foetus, the AP could be made transparent.[38,51]

Selection of participants

Seven publications focused on which foetuses should be selected for the first in-human trial based on potential risks (e.g. psychosocial development risks) and benefits (e.g. higher chances of survival).[25,27,30,47,58] According to them, EPIs of 22-23 weeks have a high mortality rate with current care and, therefore, the experimental AP treatment could be justifiable as compassionate care. EPIs of 24-25 weeks already have better survival rates, meaning that AP treatment might be even more beneficial to them, but it could also mean that the experimental treatment would be less justifiable. Four publications took an explicit stance claiming that it is acceptable to include in the trial infants so premature that without AP death or severe disability is the likely outcome.[30,55,58,59]

Included publications also focused on which parents should be involved in the clinical trial and how to counsel them to allow them to make a proper informed decision on whether to participate in the AP trial, to choose standard of treatment (i.e., intensive care), or, in countries that allow it, to choose palliative care.[37,38,44,47,58] First, AP should only be proposed to pregnant persons for whom the caesarean is already indicated and for whom it would be better not to be pregnant.[38] Second, the pregnant person (and if present the partner) should receive appropriate counselling. They should receive all necessary information related to the AP trial and the possible alternatives (i.e. intensive or palliative care), including the fact that the pregnant person will also be a research subject [38,44,47,55,58] Further, counsellors must avoid therapeutic misconception, i.e., the mistaken belief that the experimental treatment will be curative. [38,58] Counselling also needs to be nondirective[37,38] to avoid undermining pregnant people's safety for the sake of the foetus.[37,55] To this regard, Romanis and Adkins advocated for a non-fetal-centric counselling.[44] They explained that much of the literature only focuses on fetal risks, whereas AP might affect the pregnant person beyond the physical risks of the C-section, such as generating feelings of pregnancy loss and failure. Counsellors should communicate and minimize these risks, for example, by providing psychological support.[44] Finally, parents should have enough time to decide.[38,58]

Discussion

Based on our analysis of the forty-five eligible publications, we identified two main gaps in the existing literature.

Lack of consistent terminology

There is no agreement on the correct terminology for the AP subject.[15] While new terms (e.g. gestateling, fetonate) are proposed,[7] some articles refer to the AP subject as "infant".[16] Similarly, we found different terms identifying the technology itself. We chose the term artificial placenta but others refer to it as artificial womb. [60] Although all included articles discussing the moral status of the AP subject well explain and justify their terminological choices, the existence of so many different terms might be confusing. This terminological confusion is aggravated by the fact that the technology is often too ambiguously described conflating the AP with full ectogenesis. Conflating the two misrepresents how the AP functions, its applications, and the ethical issues it raises.[41,61,62] Using terms like 'artificial wombs' may suggest that APs can substitute pregnancy and create public hostility towards it. This could hinder the implementation of a potentially better treatment for EPIs.[41,57] This misrepresentation is probably most evident in the abortion debate. Those in favor of substituting abortion with AP often imply that AP can be used at any point in pregnancy,[60] or do not appropriately consider the possibilities and limitations of existing APs.[49,50] Current APs are unable to maintain EPIs of less than 22 weeks and in many cases a C-section will be necessary. Advocating for substituting abortion with AP in the current technological context would oblige pregnant persons to be pregnant longer than they wanted and to undergo a major surgery instead of opting for earlier safer and less invasive abortion. On that, we agree with Romanis and Horn that in discussing proposals that would affect people's autonomy and wellbeing so heavily, we need to either clearly state that we are speculating about a non-existing technology or refer to the description of existing technologies.[34] To clarify, we are not advocating for the end of speculative thinking. We are advocating for a more consistent and responsible use of language. One that correctly identifies the technology at hand and the related ethical issues.

Lack of ethical reflection on issues related to the first in-human trial and implementation

The AP is a clinical device being developed to treat EPIs, so the first in-human trial will inevitably involve vulnerable EPIs.[25] Furthermore, the in-human trial and implementation of the AP for EPIs are expected to occur in quick succession,[63,64] which makes the ethical reflection on the trial and implementation necessary and urgent. Despite that, only twelve out of forty-five included articles discussed research ethics and clinical-ethics issues related specifically to EPIs.

Most included articles discussed the moral status of the subject or the possibility of using the AP as an alternative to abortion or as an alternative delivery method, which will only

occur in a distant future, if it will ever occur. The AP ethical issues for EPIs and their families are currently understudied. We believe this is ethically problematic as EPIs and pregnant persons will be the ones bearing the risks of the first AP trial and implementation. We do not exclude that the AP could be used beyond its original scope, nor do we undermine the importance of discussing potential future applications of AP and their impact on pregnant people. What we found problematic is the current imbalance between the articles discussing these future scenarios and the articles discussing short-terms applications of AP. Hence, we advocate for more research on the ethical issues related to the trial and implementation of AP.

A related issue is the lack of empirical studies, particularly of studies involving prospective AP users, such as neonatal professionals or EPIs' parents. We found only two empirical studies on the topic,[65,66] of which only one involved prospective users, i.e. neonatologists.[65] The other involved reproductive rights advocates and discussed assisted reproductive technologies in general. We advocate for integrating more empirical studies on users' perspective in the development of the technology. Importantly, researchers should make an active effort to include the views of minorities, such as people with disabilities or people of colour, in their studies to ensure a comprehensive but nuanced understanding of all stakeholders' perspectives.[31] Stakeholder engagement could help produce a technology that truly answers the needs of the users. This could also help us identify potentially overlooked but important ethical issues. For example, determining the subject's moral status and name is important in the legal and academic sphere. Ambiguity in terminology and definitions might hinder communication and affect AP acceptability. Further, different moral entities have different rights and, therefore, whether the AP subject is a foetus, an infant, or a new moral entity does matter. However, scientific terms are not always appropriate in the clinical context. For example, if parents consider the AP subject "their child" clinicians should call it a child rather than gestateling, fetonate, or AP subject, even if these terms might be scientifically more correct.[15] Beyond terminological differences, this also implies that parents might perceive different ethical issues than clinicians and academics. Hence, it is important to engage with parents and other stakeholders to obtain a comprehensive understanding of the ethical issues raised by AP and to address all the relevant issues. To achieve that, though, it is important that researchers address potential obstacles to participation, especially for participants from minority groups, for example by covering the costs of transportation or by accommodating participants' requests in terms of timing and modality of data collection.[67]

Strengths and limitations

To our knowledge, this is the first review that systematically presents ethical arguments related to the AP specifically rather than discussing it along with other artificial womb or reproductive technologies. This allowed us to isolate arguments specific to the AP and to give an in-depth and nuanced overview of this debate. However, due to the narrow focus of the review and the ambiguity regarding terminology and technology description that

still permeates the ethical literature on artificial womb technologies, some articles and arguments were ineligible.

All but two publications originated from high-income western countries. Several articles had the same first authors. Six first authors are healthcare professionals; all other articles are written by scholars in ethics or law. This might limit the generalizability of results as ethical arguments are at least partially culturally sensitive. This could also indicate that despite the considerable number of included articles, the AP debate is still in its infancy and that there is not much interaction between scholars, clinicians, and developers.

Conclusions

Our review shows that the AP ethical literature is imbalanced. Most included publications focused on the possible use of AP as an alternative to abortion or healthy pregnancy instead of for the treatment of EPIs – for which it is in fact being developed and will be used. Consequently, reflection on the ethical implications of the AP for treatment of EPIs and pregnant persons is urgently needed as they will be the ones bearing the risks of the AP first.

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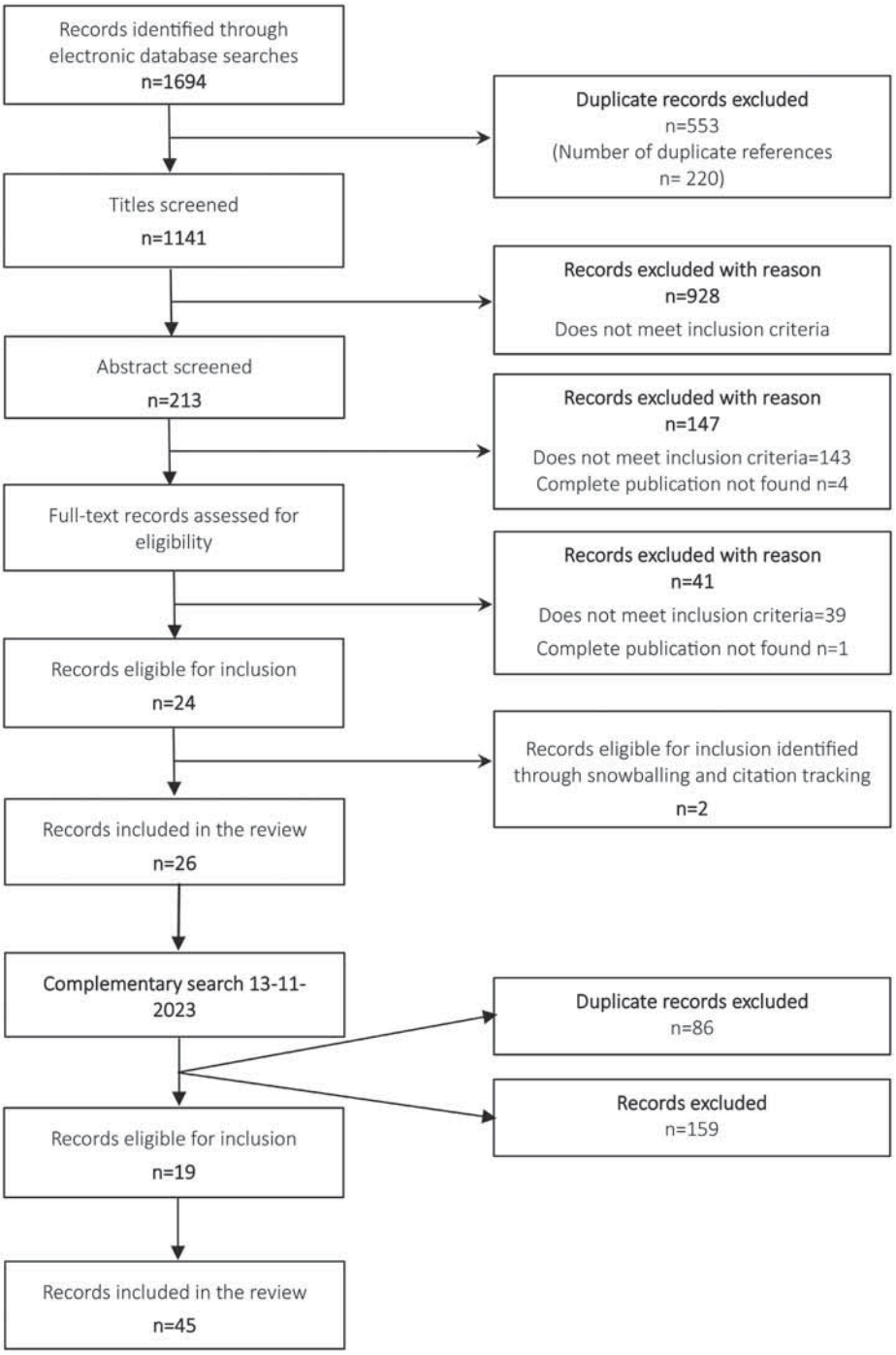

Figure 1 Process of electronic literature search for identifying and selecting articles. Flowchart is organised according to PRISMA guidelines outlined in Liberati et al.

Appendix 1 search strategy

Database	Group 1 Technology	Group 2 Ethics	Results first search (17-11-2022)	Results updated search (13-11-2023)
Medline®	artificial placenta OR artificial womb OR partial ectogenesis OR full ectogenesis OR ectogenesis OR ectogestation OR artificial womb technology OR artificial womb technologies OR artificial utero OR full ectogestation OR partial ectogestation OR biobag OR ex vivo uterine therapy OR extracorporeal life support OR extracorporeal membrane	"Ethics"[Mesh] OR "Philosophy"[Mesh] OR ethic* OR philosophy OR bioethic*[tiab] OR philosophical[tiab] OR moral[tiab] OR morals[tiab]	n=868	n=113
Embase™	'artificial placenta':ti,ab,kw OR 'artificial womb':ti,ab,kw OR 'partial ectogenesis':ti,ab,kw OR 'full ectogenesis':ti,ab,kw OR ectogenesis:ti,ab,kw OR ectogestation:ti,ab,kw OR 'artificial womb technology':ti,ab,kw OR 'artificial womb technologies':ti,ab,kw OR 'artificial utero':ti,ab,kw OR 'full ectogestation':ti,ab,kw OR 'partial ectogestation':ti,ab,kw OR biobag:ti,ab,kw OR 'ex vivo uterine therapy':ti,ab,kw OR 'extracorporeal life support':ti,ab,kw OR 'extracorporeal membrane':ti,ab,kw	ethics:ti,ab,kw OR ethical:ti,ab,kw OR philosophy:ti,ab,kw OR philosophical:ti,ab,kw OR bioethics:ti,ab,kw OR bioethical:ti,ab,kw OR moral:ti,ab,kw OR morals:ti,ab,kw	n=392	n=81
Web of Science™	All field: artificial placenta OR artificial womb OR partial ectogenesis OR full ectogenesis OR ectogenesis OR ectogestation OR artificial womb technology OR artificial womb technologies OR artificial utero OR full ectogestation OR partial ectogestation OR biobag OR ex vivo uterine therapy OR extracorporeal life support OR extracorporeal membrane	All fields: ethics OR ethical OR philosophy OR philosophical OR bioethics OR bioethical OR moral OR morals	n=396	n=64
Scopus®	TITLE-ABS-KEY: artificial AND placenta OR artificial AND womb OR partial AND ectogenesis OR full AND ectogenesis OR ectogenesis OR biobag	TITLE-ABS-KEY: ethics OR ethical OR moral OR morals OR philosophy OR philosophical OR bioethics OR bioethical	n=38	n=6

Chapter 6

Capabilities and stakeholders – Two ways of enriching the ethical debate on artificial womb technology

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Commentary

The review by De Bie et al. (2022) provides an overview of the current ethical literature on artificial womb technology (AWT).[1] Two characteristics stand out, and provide the basis for our commentary. First, the normative framework used to structure the ethical issues of AWT largely aligns with the traditional four bioethical principles: beneficence, non-maleficence, respect for autonomy and justice. We believe that the debate can be enriched by viewing AWT through the lens of a broader normative framework: the capability approach, which focuses on the freedom to achieve wellbeing. Second, the existing literature upon which the review is based, is mostly theoretical. No empirical data on stakeholders' perspectives were included, although the authors acknowledge their relevance. We believe that empirical studies are crucial in responsible innovation.

Our focus will be *narrower* than De Bie et al's in one respect: while the authors cover 4 domains in which AWT could theoretically be used, we will focus on domain III (peri-viability), because the current development of AWT is aimed at potential treatment for extreme prematurity. We think it is important to take a concrete technology as the starting-point of co-creating responsible AWT.

Capabilities: enriching the normative framework for thinking about AWT

It is common to refer to the established four principles of biomedical ethics when identifying ethical issues in healthcare. In mapping the ethical issues of AWT, De Bie et al. consistently refer to considerations that largely align with the traditional principles of biomedical ethics, with "Potential Benefits and Harms" referring to beneficence and non-maleficence; "Decision-Making Authority of Parents" and "Legal Status and Protections'' signalling respect for autonomy, and "Fairness of Access" indicating justice.[1]

We believe that the debate on AWT ethics can be enriched by embracing a broader normative framework. Crucial is the fact that wide variety exists between people regarding the extent to which they are able to *convert* certain (healthcare) means into outcomes that they value most. This might for instance be due to personal or social "conversions factors". Examples of personal factors that influence the achievement of desired outcomes include our physical condition and literacy . Examples of social conversion factors include social norms, and power relations.[2]

The capability approach, highlighting the importance of conversion factors, is a particularly well-suited framework for normative reflection on developing technologies for the purpose of health and well-being,[3] such as AWT. It is a theoretical framework centered around two normative claims. First, it is of primary moral importance for individuals to have the freedom to achieve well-being. Second, well-being should be understood in terms of "capabilities" and "functionings".[2] Capabilities refer to the real choices or opportunities available to people in leading the life they desire, while functionings are the tangible forms

of "doing" and "being" that individuals actually realize, if they so choose. By focusing on what people can actually do and be, in addition to the distribution of goods and resources, the capability approach recognizes that people can differ greatly in their ability to convert those goods and resources into real opportunities and achievements, that is, the kind of life they can effectively lead.[2]

Table 1 provides an overview of capabilities that, according to Martha Nussbaum, are central for people to live a worthy life (as judged by themselves).[4]

Table 1: Central human capabilities established by Nussbaum (2011)4

Central human capabilities established by Nussbaum:
(1) Being able to live to the end of a human life of normal length; and not have one's life reduced to not worth living.
(2) Being able to have good health (including the possibility to reproduce).
(3) Being able to maintain bodily integrity.
(4) Being able to use the senses, imagination, and think and have the ability to express yourself.
(5) Being able to have emotions and emotional attachments.
(6) Possess practical reason to form a conception of the good; being able to plan your own life or form a conception of the good.
(7) Have social affiliations that are meaningful and respectful.
(8) Express concern for other species and being able to have relationships with the natural world and to care for other species.
(9) Being able to play or laugh; to enjoy recreation activities.
(10) Have control over one's material and political environment, being able to meaningfully participate in decisions concerning one's environment.

Capabilities are helpful to formulate what – from the perspective of human flourishing – is at stake in considering AWT. For instance, the risk of dying prematurely threatens the capability of being able to live a human life of normal length (1); potential complications caused by extreme premature birth might thwart the capability of being able to have good health (2); a caesarean is needed for AWT to succeed, raising issues concerning the capability to maintain bodily integrity (3); being separated as part of the AWT procedure raises issues concerning emotional attachment (5), et cetera.

Real freedom to achieve well-being requires more than providing people with goods and means and having them choose. *Figure 1* summarizes how conversion factors may prevent or promote our real freedom (capabilities) to convert resources into desired outcomes (functionings), if we so choose.

Figure 1. The relation between resources, capabilities and functioning; based on Robeyns (2005).5

This has direct implications for how to deal with the traditional four medical-ethical principles. First, it shows that caring about beneficence and non-maleficence, and an optimal

balance between the two, requires accounting for positive and negative conversion factors. That is also crucial for respecting autonomy and for acting justly. For even if equal access to AWT is guaranteed (justice, as interpreted by De Bie et al.)[1], this does not mean that only an informed choice is standing in the way of a person's wellbeing. The freedom to achieve wellbeing at the very least requires remedying negative conversion factors, also a matter of justice.

The following examples from domain III (peri-viability) show how the capability approach can complement the results of the review of De Bie et al.[1] Regarding justice, while the authors focus on fair access to AWT, broader considerations of justice also include questions like whether society should invest in improving antenatal care instead of developing AWT. If promoting real freedom to achieve wellbeing is our aim, AWT is one option among several others.

Beneficence and non-maleficence are mostly discussed in (narrow) medical-technical terms, focusing e.g., on the viability of the foetus and potential complications of extreme prematurity. The capability approach places these considerations in the context of human flourishing, providing a more comprehensive and nuanced perspective on the potential effects of AWT on the foetus and the mother. It also enriches the interpretation of pros and cons of the technology by thinking through conversion factors that could hamper our freedom to achieve well-being. For example, what if you survive with handicaps through AWT, but later in life medical and social support is insufficient (sociopolitical conversion factor). It shows that AWT is not a stand-alone solution but needs to be incorporated in a broader system of healthcare.

De Bie et al's discussion of "Decision-Making Authority of Parents'' focuses on the autonomy of the pregnant person.[1] However, the capability approach recognizes that social norms and expectations (e.g., about responsibilities), as well as power relations and pressure can be sociopolitical conversion factors that can hinder the pregnant person's freedom to achieve well-being. These are relevant ethical issues (e.g., in the context of the necessary caesarean), even if they do not preclude being able to provide informed consent.

In sum: the capability approach allows for a richer and more comprehensive normative evaluation of AWT, compared to the traditional four principles.

Stakeholders: enriching the ethical debate on AWT with empirical research

The ethical debate about AWT can also be enriched by including empirical ethical research. We believe this is a crucial element of responsible innovation. Constructively engaging various stakeholders in an early stage allows us to identify potential concerns, and to ensure that the technology is developed and used in line with relevant ethical values and considerations.

A Guidance Ethics Approach (GEA) is well-suited for investigating what is of moral significance in developing and using AWT according to directly affected stakeholders.[6] GEA recognizes that technology can have a large impact on society and individuals, and therefore seeks to ensure that its development is guided by ethical considerations and is aligned with stakeholders' values as much as possible.

The GAE typically takes the form of a stakeholders' workshop with representatives of patient groups, (medical) professionals, technologists and managers/policy-makers. Participants go through three stages, and provide the normative content. *Figure 2* provides an overview. .

Figure 2 The process of Guidance Ethics6

A Guidance Ethics workshop results in:

- A clear description of a concrete technology and the context in which it can be used (Stage 1: Technology in context);
- A list of (a) actors whose viewpoint should (also) be taken into account, (b) potential effects of using the technology in this context, and (c) which values are at play (Stage 2: Dialogue);
- A list of options for action (Stage 3) that could support responsible innovation, by changing the technology (*ethics by design*), by changing the 'environment' in which the technology is used (e.g., issuing guidelines) (*ethics in context*), and/or by empowering those using the technology e.g., through learning new skills (*ethics by user*).[6]

Guidance ethics⁺: combining guidance ethics workshops with the capability approach

The capability approach enriches the ethical landscape of AWT. It invites us to look at relevant conversion factors, with the aim to promote the individuals' real freedom to lead fulfilling lives, as judged by themselves. The latter requires empirical ethical research. The GEA provides a structure for constructively including the viewpoints of stakeholders. This will help to examine which capabilities and functionings are particularly important in the case of AWT, and which options for action could promote the desired functionings as identified by the stakeholders.

We call the combination of the Guidance Ethics Approach with a substantive normative framework such as the capability approach: Guidance Ethics⁺. This approach will be taken in a project on AWT in which Leiden University Medical Center and Radboud University Medical Center cooperate.

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Intermezzo C:

Rapport Workshop Begeleidingsethiek (In Dutch)

Angret de Boer & André Krom

Inleiding

Op 7 april 2023 werd een eerste workshop begeleidingsethiek gehouden over de ontwikkeling van een artificiële placenta[2] als mogelijk toekomstige behandeling bij extreme vroeggeboorte op de grens van levensvatbaarheid. De workshop werd georganiseerd in het kader van het ZonMw project *'On the limits of neonatal viability: the ethics of changing towards an individualized prognosis-based approach'*.[3] Doel van de workshop was om een gestructureerd gesprek/dialoog te voeren met relevante betrokkenen over ethische aspecten rondom de ontwikkeling van deze technologie.

Met behulp van de Aanpak begeleidingsethiek is in de workshop van 7 april o.a. gekeken naar de mogelijke effecten van de ontwikkeling en het mogelijke gebruik van de artificiële placenta, en welke waarden daarbij een rol spelen. Vervolgens is geïnventariseerd welke handelingsopties er zijn om de positieve effecten waar mogelijk te versterken en eventuele negatieve effecten op belangrijke ethische waarden te beperken.[4]

Aan de workshop namen 23 mensen deel (incl. moderator en subgroep moderatoren). Dit waren onder andere mensen met verschillende medische en technische achtergronden, ethici, juristen, ouders, patiëntenvereniging Care4Neo en vertegenwoordigers uit de wereld van beleid (zie Bijlage 1 voor ene overzicht van de deelnemers). Daarmee was het een goede groep om de dialoog te voeren over dit onderwerp. De workshop werd gefaciliteerd door een moderator van de afdeling Ethiek en Recht van de Gezondheidszorg van het LUMC.

Aanpak begeleidingsethiek en opzet workshop

De Aanpak begeleidingsethiek is ontwikkeld door de werkgroep ethiek en digitalisering van ECP (Platform voor de Informatiesamenleving). De werkgroep werd voorgezeten door Peter-Paul Verbeek (voorheen Universiteit Twente) en Daniël Tijink (ECP). In 2019 schreven zij de publicatie *Aanpak Begeleidingsethiek*.[5] Workshops begeleidingsethiek duren 3,5 – 4 uur en hebben een vaste opzet die ertoe leidt dat verschillende aspecten van de casus in kaart worden gebracht.

De workshop volgde de Aanpak zoals weergegeven in onderstaande afbeelding (*Figuur 1*).[6]

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2 De kunstmatige of artificiële placenta wordt ook wel *Artificial Amniotic sac and Placenta Technology* (AAPT) genoemd.

3 De workshop is onderdeel van de ZonMw klinische fellowship beurs van Dr. E.J.T. Verweij (LUMC) en van het promotieonderzoek van A. de Boer (LUMC/ Radboudumc).

4 De resultaten van de workshop zullen o.a. aangeboden worden aan het Perinatal Life Support (PLS) consortium binnen Europa en er zal een wetenschappelijk artikel over verschijnen.

5 https://begeleidingsethiek.nl/over-het-platform/

6 Bron: https://ecp.nl/project/aanpak-begeleidingsethiek/

Figuur 1: Overzicht Aanpak begeleidingsethiek

Een workshop begeleidingsethiek bestaat uit de volgende fasen:

Fase 0: Introductie

- Het bespreken van de doelstelling van de Aanpak begeleidingsethiek en een toelichting op de Aanpak en het gedachtegoed daarachter.

Fase 1: Technologie in context

- Een toelichting op de technologie en de context waarin deze mogelijk zal worden gebruikt. Hier krijgen de deelnemers de gelegenheid aanvullende/verhelderende vragen te stellen.

Fase 2: Dialoog

- Een korte ronde waarin deelnemers aan de workshop *Actoren*[7] benoemen die met de technologie te maken kunnen krijgen;
- Deelnemers benoemen en bespreken mogelijke positieve en negatieve *Effecten* die gebruik van de technologie zou kunnen hebben;
- Deelnemers benoemen *Waarden* die een rol spelen bij die effecten. Welke waarden worden naar verwachting bevorderd als de technologie gebruikt wordt en welke waarden komen mogelijk juist op het spel te staan?

7 Ook wel veldpartijen, spelers of stakeholders genoemd.

Fase 3: Handelingsopties

- Deelnemers gaan op zoek naar handelingsopties om positieve effecten van de technologie te bevorderen, negatieve effecten te voorkomen of zoveel mogelijk te beperken. Daardoor kunnen belangrijke waarden worden beschermd of bevorderd.
- Deelnemers zoeken naar handelingsopties vanuit drie invalshoeken:
  - Wat kun je aan de *Technologie* zelf veranderen?
  - Wat kun je veranderen in de fysieke, sociale of institutionele *Omgeving* waarin de technologie mogelijk zal worden gebruikt?
  - Wat vraagt verantwoord *Gebruik* van de technologie van degenen die de technologie gaan gebruiken?

Bij enkele onderdelen zijn kleine aanpassingen gedaan ten opzichte van hoe de Aanpak veelal wordt toegepast. In het verslag zal steeds worden toegelicht welke aanpassingen zijn gedaan.[8]

De workshop werd opgenomen, zowel de plenaire onderdelen als de gesprekken die in subgroepen werden gevoerd over effecten, waarden en handelingsopties. Deze opnames werden getranscribeerd door een professioneel bureau en gebruikt om dit verslag op te stellen. Nadat de transcripten werden ontvangen, zijn de opnames definitief gewist. De transcripten zijn geanonimiseerd uitgetypt. Zo is geborgd dat de quotes die in dit verslag zijn opgenomen niet direct te herleiden zijn naar de persoon die dit heeft gezegd tijdens de workshop.

Fase 1: Technologie en context

Casus: technologie in context

Om te begrijpen welke ethische aspecten komen kijken bij het gebruik van een technologie en hoe je daar verantwoord mee om zou kunnen gaan, is het belangrijk om meer te weten over de technologie zelf en in welke context de technologie (mogelijk) gebruikt zal gaan worden.

Ter voorbereiding van de workshop op 7 april 2023 ontvingen de deelnemers een casusbeschrijving over de artificiële placenta. Tijdens fase 1 kregen de deelnemers de gelegenheid aanvullende vragen stellen over de ontwikkeling van deze technologie en in welke context dit gebruikt zou kunnen worden.

8 In Bijlage 2 wordt vervolgens toegelicht *waarom* deze aanpassingen zijn gedaan. Het systematisch bijhouden welke aanpassingen zijn gedaan en waarom maakt het mogelijk om te leren of en zo ja welke aanpassingen in de Aanpak begeleidingsethiek bij kunnen dragen aan het zo goed mogelijk ethisch begeleiden van de ontwikkeling van (nieuwe) technologie, enerzijds, en het zo goed mogelijk begeleiden van de maatschappij bij de omgang met nieuwe technologische mogelijkheden zoals de artificiële placenta, anderzijds.

De ontwikkeling van de artificiële placenta heeft als doel om sterfte en ziekte rondom de geboorte te verminderen.[9] De technologie bootst de omgeving en functie van een vruchtzak, het vruchtwater en de placenta na. Hierdoor blijft de 'perinaat'[10] in de artificiële placenta fysiologisch gezien in de staat van een foetus. In Tekstbox 1 staat de informatie die de deelnemers voorafgaand aan de workshop hebben ontvangen.

De artificiële placenta als mogelijke behandeling bij extreme vroeggeboorte

Gevolgen van extreme vroeggeboorte

In Nederland worden jaarlijks 2-4 van de 1000 baby's te vroeg geboren (<28 weken zwangerschapsduur). Na de geboorte wordt de baby opgenomen op de Neonatale Intensive Care Unit (NICU) waar behandeling wordt gestart, bijvoorbeeld door middel van beademing en sondevoeding, en de baby's in een couveuse liggen.

Hoe vroeger het kind wordt geboren, hoe meer kans het heeft op complicaties en gevolgen van de vroeggeboorte en de behandeling. Met de huidige behandeling bij een geboorte na 24 weken zwangerschap blijven ongeveer 50 van de 100 baby's die opgenomen worden op de intensive care in leven; ongeveer 50 van de 100 baby's overlijden. Als de baby overleeft na 24 weken zwangerschap, hebben van de 100 baby's op basisschoolleeftijd: 67 geen handicaps of een milde handicap, en daarnaast een verhoogde kans op problemen op school, 16 een matige handicap, en 17 een ernstige handicap. Om het ontwikkelen van deze complicaties te verminderen, en de overleving en kwaliteit van leven van deze groep kinderen te verbeteren, wordt nagedacht over het gebruik van de zogenaamde artificiële ('kunstmatige') placenta.

De artificiële placenta: het alternatief voor de couveuse

De artificiële placenta is een afgesloten, verwarmde omgeving met kunstmatig vruchtwater. Via de artificiële placenta krijgt de foetus zuurstof en voedingstoffen binnen en wordt er gestreefd naar verdere groei en (uit)rijping van organen in een situatie vergelijkbaar met die in het lichaam van de zwangere vrouw. Het doel van de artificiële placenta is de groep kinderen die te vroeg geboren wordt een betere kwaliteit van leven te geven, met minder (ernstige) handicaps. De artificiële placenta is dus bedoeld als vervanging van de huidige (couveuse)behandeling bij extreem vroeg geborenen.

Tot op heden is er alleen onderzoek gedaan naar de artificiële placenta met diermodellen. In 2017 zorgde een Amerikaanse onderzoeksgroep voor wereldnieuws. Zij waren er na jarenlang onderzoek in geslaagd om lammetjes vier weken te laten groeien in een artificiële placenta. Deze lammetjes waren bij plaatsing in de artificiële placenta in hun ontwikkeling te vergelijken met een menselijke foetus van 24 weken en werden uiteindelijk gezond 'geboren' uit de kunstmatige 'placenta'.

Onderzoek naar de artificiële placenta bij mensen

De verwachting is dat er binnen een aantal jaar gestart kan worden met verder onderzoek naar het opvangen van extreem prematuur geboren baby's in de artificiële placenta. In verschillende landen zijn ze bezig met het ontwikkelingen van deze nieuwe techniek.

De ontwikkeling van de artificiële placenta biedt kansen om de behandeling van extreem prematuur geboren kinderen te verbeteren. Tegelijkertijd roept de ontwikkeling van de artificiële placenta ethische, juridische en maatschappelijke vragen op, over bijvoorbeeld de onzekerheid die bestaat over de effectiviteit en de veiligheid van de artificiële placenta, dat er mogelijk een keizersnede noodzakelijk is en wat het betekent voor de hechting tussen ouders.

Tekstbox 1: Informatie die deelnemers voorafgaand aan de workshop kregen over de ontwikkeling en het mogelijke gebruik van de artificiële placenta

9 Sterfte en ziekte rondom de geboorte wordt ook wel perinatale mortaliteit en morbiditeit genoemd.

10 Verschillende benamingen in de literatuur bekend voor hetgeen er in de artificiële placenta zit, zoals perinaat, gestatialing, fetonate. In dit verslag gebruiken wij de term perinaat.

Verhelderende vragen over de technologie in context

In een korte presentatie over de artificiële placenta en de context waarin deze technologie in eerste instanatie zou kunnen worden gebruikt/onderzocht, werd o.a. aangegeven dat de perinaat vanuit de artificiële placenta bij 28 weken overgeplaatst zou worden naar een reguliere couveuse. Dat zou betekenen dat de artificiële placenta niet in de plaats komt van behandeling in de couveuse, maar dat de periode in de artificiële placenta vooral gevolgen zou kunnen hebben voor de behandeling in de couveuse, die daardoor mogelijk minder ingrijpend kan worden.

Na de presentatie konden deelnemers verhelderende vragen stellen. Hieronder vindt u een kort overzicht van welke thema's daarbij aan bod zijn gekomen. De vragen zijn beantwoord met behulp van één van de deelnemers die deel uitmaakt van het Nederlandse consortium die zich richten op de ontwikkeling van een prototype van de artificiële placenta. Deze deelnemer kon de meer technische vragen van overige deelnemers beantwoorden.

Focus ligt op toepassing vanaf 24 weken

Bij de ontwikkeling van de artificiële placenta in Nederland wordt er vooralsnog van uit gegaan dat een kindje vanaf 24 weken in de artificiële placenta zou worden geplaatst. In het buitenland en in de wetenschappelijke literatuur wordt het verlagen van deze grens naar bijvoorbeeld 22 weken gesproken. In Nederland is dat vanuit het consortium vooralsnog niet het doel.

Vaginale geboorte of keizersnede

Bij het ontwerpen van de artificiële placenta is het *uitgangspunt* dat het kind na een vaginale geboorte in de artificiële placenta wordt geplaatst. Het idee is dat het kind geboren wordt in een zak die gevuld is met kunstmatig vruchtwater en daar de navelstreng aangeprikt wordt. 'Dan wordt het kindje met zak en al in een soort […] couveuse geplaatst, waar de zak gevuld met kunstmatig vruchtwater kan worden bevestigd.' De vaginale partus zou in een bed of een bevalbed moeten kunnen plaatsvinden. Dit is geoefend met een Concord-tafel.

Insteek is om te voorkomen dat een keizersnede per se noodzakelijk is, het zou allebei moeten kunnen en bij voorkeur een vaginale partus. Of dat inderdaad allebei kan, en of de ene optie misschien betere uitkomsten zou kunnen geven dan de andere, is vooralsnog onbekend. Het is denkbaar dat een keizersnede voor zo goed mogelijke uitkomsten voor het kind een meer gecontroleerde omgeving biedt voor de transitie naar de artificiële placenta: *'Het achtjarig onderzoek wat we nu aangevraagd hebben zou mee moeten helpen om die vraag te beantwoorden. In welke van de situaties zou welke van de bevallingen geschikt zijn? Het antwoord kan zijn dat in alle situaties een van de twee precies geschikt is. Dat weten we niet. Het is dus een uitgangspunt, maar daar zit nog een stuk aannames in.'*

Wanneer de transitie eenmaal is ingezet - dus een eerste ademteug – is de vraag of overplaatsing naar een artificiële placenta nog mogelijk is: *'Nee, precies. Dat maakt de vraag*

van hoe realistisch [het] [is] bij een vaginale bevalling, natuurlijk wel een hele spannende. Of je niet toch gaat uitwijken naar de keizersnede. De transitie gebeurt natuurlijk eigenlijk al voordat je geboren wordt. Dat is [...] een vraag waar we geen antwoord op hebben. Het is wel duidelijk dat die vaginale route - ondanks die prachtige Concord-tafel - wel echt ingewikkeld is.'

Veilige toepassing bij mensen hangt af van de mogelijkheden en beperkingen van dierproeven

Vooralsnog zouden kinderen met 28 weken vanuit de artificiële placenta worden overgeplaatst naar een couveuse. Dat hangt samen met de mogelijkheden en beperkingen van dierproeven die momenteel worden gedaan om de veiligheid van de artificiële placenta te onderzoeken. Deze studies worden gedaan met lammetjes tot vier weken oud. Na vier weken zijn lammetjes volgroeid. Na die tijd worden de lammetjes uit de artificiële placenta gehaald. Omdat ze dan volgroeid zijn, worden ze niet in een couveuse geplaatst. Voor onderzoek naar de veiligheid van de artificiële placenta voor de mens levert dit een beperking op. Vertaald naar de mens staan die 4 weken bij lammetjes namelijk voor een zwangerschap van 28 weken. Het is momenteel niet mogelijk om op basis van dierproeven iets te zeggen over de veiligheid van de artificiële placenta voor kinderen ouder dan 28 weken. In theorie zouden dierproeven met niet-humane primaten kunnen worden gedaan, maar ook daar kleven ethische vragen aan. Dat is één van de redenen waarom kindjes vooralsnog na 28 weken uit de artificiële placenta zouden worden overgeplaatst naar een couveuse. Deze terughoudendheid hangt ook samen met een andere ethische vraag: is het ethisch om na 28 weken te zeggen dat we kinderen de huidige therapie (de NICU-behandeling zoals die nu is) kunnen bieden? Is dat beter, even goed of slechter dan wat de artificiële placenta zou kunnen bieden? 'We hebben daar vooralsnog geen antwoord op.'

De navelstreng als toegangspoort

Als een kindje in de artificiële placenta zou worden geplaatst, dan worden zuurstof en voedingsstoffen voor het kindje via de navelstreng toegediend. De navelstreng is de toegangspoort. Dat biedt ook mogelijkheden tot medische controles. De aansluiting op een kunstmatige placenta biedt bijvoorbeeld ook de mogelijkheid om monitoring van bloedgassen te doen en om concentraties van stoffen in het bloed te meten. Op basis van weer andere monitoringsmogelijkheden – zoals een echo – zouden desgewenst ook andere zaken die je wilt monitoren, kunnen worden toegevoegd.

Medische handelingen in de artificiële placenta

Het is vooralsnog een open vraag of, en zo ja welke medische handelingen mogelijk en wenselijk zijn als een kindje in de artificiële placenta is geplaatst.

Meerlingen

Een derde van de groep extreme vroeggeboortes op de NICU zijn tweelingen. In theorie zou de artificiële placenta ook voor meerlingen geschikt kunnen zijn. Wel is de vraag hoe dit technisch gerealiseerd zou kunnen worden. Voor een dergelijke situatie is vooralsnog

geen goed diermodel beschikbaar. Het is dus niet mogelijk om op basis van dierproeven iets te zeggen over de veiligheid van toepassingen bij menselijke meerlingen.

Naast technische vragen spelen hierbij ook (aanvullende) ethische vragen een rol. Bijvoorbeeld: wat als de mogelijkheid van plaatsing in een artificiële placenta maar voor één van de kinderen uit een meerling aangeboden zou kunnen worden?

Hoe ver weg is dit? Hoe snel?

In Nederland is een consortium opgericht die werkt aan de ontwikkeling van de artificiële placenta. Het project in Nederland moet in 2024 een technisch werkzaam prototype opleveren. In Amerika lopen ze technisch gezien voor op Europa. Een groep uit Philadelphia zit met hun onderzoek bijvoorbeeld in ronde negen van beoordeling door de FDA (de U.S. Food and Drug Administration). Zij moeten de technische testen bij de FDA laten doorlopen. Zij verwachten dat op korte termijn - ergens in de komende paar jaar - in Philadelphia de eerste mens in de artificiële placenta gaat. 'Die zijn echt wel heel erg ver.'

Fase 2: Dialoog

In de dialoogfase gingen de deelnemers in gesprek over wie er betrokken zijn en zouden kunnen zijn bij de ontwikkeling en het mogelijke gebruik van de artificiële placenta. Daarnaast bogen zij zich over positieve en negatieve effecten van het gebruik van de artificiële placenta, en over belangrijke waarden die daarbij een rol spelen. Deze waarden worden expliciet gemaakt om er zo goed mogelijk rekening mee te kunnen houden bij het eventuele gebruik van de artificiële placenta.

Actoren

Bij het onderwerp 'actoren' is de vraag wie er betrokken is, of op wie het gebruik van de artificiële placenta invloed heeft of zou kunnen hebben. De deelnemers aan de workshop vertegenwoordigen zelf al een aantal verschillende actoren. Aan hen werd gevraagd wie zij dachten dat er nog meer betrokken zijn, of zouden moeten worden. Deelnemers kregen eerst enkele minuten de tijd om voor zichzelf op post-its te schrijven aan welke actoren zij dachten. Dit is daarna plenair besproken. Tabel 1 geeft een overzicht van welke actoren werden genoemd tijdens de workshop van 7 april.[11] Bij een aantal actoren is een treffende quote of een korte toelichting ogenomen.

11 Tijdens de plenaire bespreking zijn de meeste actoren die deelnemers op post-its hadden genoteerd, genoemd, maar niet alle. Na de workshop zijn alle post-its verzameld en zijn ook actoren die niet plenair werden genoemd, zoveel mogelijk in de tabel gezet. Als niet precies duidelijk was wat bedoeld werd, is er voor gekozen om de input niet in de tabel te zetten, maar in een voetnoot. Dat geldt bijvoorbeeld voor 'Een diverse populatie kinderen'.

Tabel 1 Actoren zoals benoemd door deelnemers aan de workshop op 7 april 2023

Categorie	Genoemde actoren
Familie	Zwangere[12] Gezonde zwangeren Partner Kind zelf/foetus[13] Broers en zussen (*siblings*) Bredere familie (bv. opa's, oma's) Gezondere voldragen kinderen[14] Oud-patiënten (m.n. die met complicaties) Ouders van tweelingen Ongewenst kinderloze stellen Patiëntenorganisaties die ouders en patiënten vertegenwoordigen
Zorg	Verschillende artsen: gynaecologen, neonatologen[15], kinderartsen op de follow-up poli, oogartsen (i.v.m. kans op retinopathie[16]), huisartsen, perfusionisten[17] Verpleegkundigen Psychologen Verloskundigen Medisch maatschappelijk werkers[18] Geestelijk verzorgers[19] Pedagogen Beroepsverenigingen, zoals de Nederlandse Vereniging voor Obstetrie en Gynaecologie (NVOG) en de Nederlandse Vereniging voor Kindergeneeskunde (NVK)
Techniek & Data	Techniekontwikkelaars/ingenieurs Technische dienst ziekenhuizen/medische techniek Logistiek medewerkers

12 *'Er wordt nu gezegd: ouders. Ik zou zelf een moeder en de partner uit elkaar halen. (...) Vooral omdat de vrouw eventueel de keizersnede ondergaat. Dus zijn het, wat mij betreft, twee aparte mensen in dat opzicht.'*

13 '*Het perspectief van de foetus zou ik centraal zetten hierbij, dat vind ik essentiee*l.'

14 Als de artificiële placenta een betere omgeving zou vormen en daardoor kinderen zich ontwikkelen onder de beste omstandigheden en daardoor 'gezonder' geboren worden.

15 Neonatologen geven zorg aan te vroeg geboren kinderen of aan zieke kinderen die net geboren zijn.

16 Retinopathie betekent beschadiging van het netvlies (retina = netvlies).

17 Een perfusionist bedient de hart-longmachine. Een hart-longmachine neemt de functie van het hart over tijdens een operatie.

18 Medisch maatschappelijk werkers bieden psychosociale begeleiding aan patiënten en hun naasten bij problemen die te maken hebben met ziekte, behandeling en/of een ziekenhuisopname.

19 Geestelijk verzorgers komen in beeld als de vanzelfsprekende orde van het alledaagse leven wordt doorbroken; in situaties van leven en dood, bij afscheid en verlies, bij ervaringen van grote verbondenheid of juist van verlatenheid, en bij ethische vragen. Zij zijn deskundig in het omgaan met levensvragen, zingeving, spiritualiteit en ethische afwegingen. Bron: Vereniging van Geestelijk Verzorgers.

Tabel 1 Continued

Categorie	Genoemde actoren
Beleid	Medisch tuchtcollege Beleidsmakers Adviesraden, zoals de Raad voor de Volksgezondheid (RVS) Wetgevers Food and Drug Administration (FDA; Verenigde Staten) Commissies die CE-markering toetst Het ministerie van Volksgezondheid, Welzijn en Sport Juristen Politiek
Wetenschap	Wetenschappers[20] Sociologen[21] Ethici Fysiologen[22] Proefpersonen (ouders/kind) Proefdieren[23]
Financiering	Zorgverzekeraars Zorginstituut Nederland
Toezicht	Medisch Ethische Toetsings Commissie (METC) Centrale Commissie Mensgebonden Onderzoek (CCMO) Inspectie Gezondheidszorg en Jeugd (IGJ) Datamanager
Commerciële partijen	Commerciële partijen[24] Fabrikanten Leveranciers materiaal
Pers	De pers
Overig	Goede doelen Burgers/premie betalers/maatschappij Mensen in landen waar dit mogelijk niet beschikbaar zal zijn Gelovigen/kerken Leerkrachten Activisten: o.a. feministen, anti-abortus bewegingen

20 *'Zowel wetenschappers die aan de artificiële placenta werken, als anderen naar wie het geld dus niet gaat'*

21 Sociologen bestuderen sociale relaties tussen mensen en het gedrag van mensen in de samenleving.

22 Fysiologen bestuderen hoe moleculen, cellen, organismen en mensen (biologisch) functioneren.

23 Voordat onderzoek mag worden gedaan naar de artificiële placenta bij mensen moet eerst uit onderzoek blijken dat het voor proefdieren veilig i*s.*

24 *'Er zijn misschien ook bedrijven die hieraan verdie*nen?'

Actiepunten

Onderdeel van de Aanpak begeleidingsethiek is om partijen die geraakt kunnen worden door het ontwikkelen en het gebruik van een technologie, zoveel mogelijk te betrekken bij het ontwikkelen en implementeren van die technologie. Of, als dat niet lukt, hun perspectief daarin zo goed mogelijk mee te nemen.

Dat levert twee actiepunten op. Ten eerste om partijen uit Tabel 1 te betrekken wiens perspectief nog geen plek heeft kunnen krijgen bij het ontwikkelen en implementeren van de artificiële placenta; en ten tweede om actief te blijven zoeken naar partijen die eventueel nog missen.

Effecten

De vraag in dit onderdeel is standaard welke effecten het gebruik van een technologie zou kunnen hebben, zowel positief als negatief. In totaal zijn er tijdens de workshop aanvankelijk 67 mogelijke effecten benoemd, waarvan 17 positieve en 50 negatieve effecten.[25] Ten behoeve van het verslag zijn de effecten nader geordend (zie Tabel 2):

- Enkele punten die door de deelnemers werden genoemd waren in eerste instantie niet altijd expliciet als effect benoemd, maar als vraag. Uit die vragen werd steeds duidelijk dat de deelnemers wel specifieke positieve of negatieve effecten in gedachten hadden. In die gevallen zijn de vragen geherformuleerd in termen van effecten.[26]
- De effecten zijn opgedeeld in een aantal thema's, namelijk effecten op het kind (tabel 4a), op de ouders/ouder-kind band (tabel 4b), op de zwangere/zwangerschap/geboorte (tabel 4c), op de zorg (tabel 4d), op de techniek (tabel 4e), op wetenschappelijk onderzoek (tabel 4f) en overige effecten (tabel 4g).
- Soms werden dezelfde effecten in verschillende formuleringen naar voren gebracht. In het uiteindelijke overzicht van effecten, zijn deze samengevoegd.[27]
- Tot slot was bij nadere beschouwing bij enkele effecten onvoldoende duidelijk welke mogelijke gevolgen deelnemers precies in gedachten hadden. In die gevallen zijn deze effecten niet opgenomen in Tabel 2.[28]

Na het samenvoegen en verwijderen van een aantal genoemde effecten, blijven er in totaal 50 mogelijke effecten over, waarvan 10 positieve en 40 negatieve effecten. Bij een aantal effecten is een treffende quote of een korte toelichting opgenomen.

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25 De oorspronkelijke lijst met effecten zoals benoemd door de deelnemers tijdens de workshop is te vinden in Bijlage 2.

26 Deelnemers zijn in de gelegenheid gesteld om feedback te geven op het concept verslag, o.a. om te borgen dat hun input goed in het uiteindelijke verslag is verwerkt.

27 Een overzicht van welke effecten zijn samengevoegd vindt u in Bijlage 3.

28 Om welke effecten het gaat, is te vinden in Bijlage 3.

Tabel 2a Positieve en negatieve effecten van het gebruik van de artificiële placenta op het kind zoals benoemd door deelnemers aan de workshop op 7 april 2023

Positief	**Negatief**
KIND	
1. De foetale fysiologie wordt gehandhaafd	
	2. Vertechnisering van geboorte en het kraambed
3. Minder schade aan orgaansystemen	4. Meer schade aan orgaansystemen
	5. Onzekerheid/onbekendheid over uitkomsten, waardoor je een beslissing moet nemen zonder dit te kunnen baseren op bekende uitkomsten.[29]
6. Het voorkómen van (over)'strekken' dat nu vaak optreedt als een kind lange tijd in de couveuse heeft gelegen	7. Minder goede bewegingsontwikkeling van het kind en het missen van het effect van beweging van de moeder.[30]
8. Minder pijnlijke handelingen dan in de couveuse, zoals steeds prikken, waardoor er minder stress ontstaat voor de pasgeborene[31]	
9. Betere kwaliteit van leven[32]	10. Slechtere kwaliteit van leven[33]
11. Betere overlevingskansen (levensreddend)[34]	12. Overlevende baby is niet altijd 'goed'

29 *'Ik vind het nog steeds moeilijk om voor te stellen. Dat je eerst 28 weken in de artificiële placenta zit en dan daarna in de gewone couveuse. Ik vind het heel moeilijk om voor te stellen. Ik maak me nog steeds heel erg bezorgd om die kinderen. Daarvoor weet ik gewoon onvoldoende. Ik vraag me af waarom iedereen er nu zo positief over is. Hoe weet je nou dat ze het allemaal zoveel beter gaan doen? Die onzekerheid voor mij maakt het heel moeilijk om door te de*nken.'

30 *'Hoe gaat dit in de artificiële placenta? Kan dit worden nagebootst? [Wat zijn de] effecten op [de] lange termi*jn?'

31 *'Als kinderen geboren zijn met 24 of 28 weken, hebben zij heel veel pijnlijke behandelingen. Soms 20 tot 30 per dag. Als dat minder zou worden met deze techniek, zou dat enorme positieve effecten opbreng*en.'

32 Als toelichting werd gegeven dat minder schade aan orgaansystemen zou optreden, dat vroeggeboorte minder negatieve effecten zou hebben dan nu en dat sprake zou zijn van minder morbiditeit.

33 Als toelichting werd gegeven dat meer schade aan orgaansystemen zou optreden, dat vroeggeboorte meer negatieve effecten zou hebben dan nu en dat sprake zou zijn van meer morbiditeit.

34 *'Als ik mijn kind [hiermee] had kunnen redden, had ik gezegd: ja, doe alles. Doe alles om mijn kind te redde*n.'

Tabel 2b Positieve en negatieve effecten van het gebruik van de artificiële placenta op de ouders en de ouder-kind relatie zoals benoemd door deelnemers aan de workshop op 7 april 2023

Positief	Negatief
OUDERS/OUDERS-KIND	
	13. Complexere keuzes voor ouders - De techniek biedt hoop waar die nu misschien niet is, maar mogelijk brengt het aangrijpen van die hoop veel schade met zich mee.[35] - Er ontstaat meer valse hoop[36]
	14. Ouders voelen zich minder vrij om nee te zeggen tegen de techniek, en durven minder snel te kiezen voor zwangerschapsbeëindiging of comfort care[37]
	15. Meer onduidelijkheid over de lange termijn effecten van deze behandeling op ouders[38]
	16. Het kan een angstig gedachte en/of beeld voor ouders zijn dat hun kind in een artificiële placenta zit gepaard met meer onzekerheid of het wel goed gaat
	17. Verandering van het beeld van ouderschap[39]
	18. De rol van de partner van de zwangere verandert, waarbij de verantwoordelijkheid voor het kind tot de geboorte meer wordt verdeeld.
	19. Niet/minder betrokken zijn bij de zorg voor je kind - Effecten van het niet kunnen verzorgen - Het niet kunnen buidelen[40] - Niet kunnen praten/zingen tegen je kind ('geen geluiden') - Minder mogelijkheden tot gezinsvorming (vergeleken met de huidige NICU behandeling) en de gevolgen daarvan voor imprint foetus[41]
	20. Het leidt tot meer wat-als vragen wanneer het kind het niet heeft gered wat kan leiden tot meer schuldgevoel, spijt en/of schaamte als het kind het niet redt en de ouders de keuze met terugwerkende kracht niet naar zichzelf kunnen verantwoorden.
	21. Slechtere rouwverwerking als het kind het niet redt, omdat er dan geen (of minder) contact is geweest

35 '*Hoe groter de keuze, hoe lastiger het wordt om te beslissen*'

36 '*Als dit er was geweest, dan hadden we gelijk gezegd: we doe*n *het.*'

37 '*Voel je je als ouder vrij om nee te zeggen tegen de techniek? Durven [zij nog] te kiezen voor zwangerschapsbeëindiging of comfort c*are?'

38 Dit draagt bij aan de complexiteit van de besluitvorming. Bovendien is bekend dat de huidige NICU-behandeling grote invloed heeft op het leven van ouders. Mogelijk blijft dit effect ook met de artificiële placenta bestaan.

39 '[Eerst ben je] ouder van een ongeboren kind, dan ben je ouder van een perinaat (in de artificiële placenta) en pas dan ben je ouder van een pasgeborene.

40 Bij buidelen of kangoeroeën wordt de baby met alleen een luier aan op de blote borst van de ouders gelegd, waardoor huid op huid contact ontstaat. Dat heeft zowel voor het kind als de ouders voordelen op de korte en de lange termijn. Zie daarover bijv. de informatie over Kangoeroeën/buidelen op de website van Care4Neo.

41 '*Ik had gelezen dat op de NICU ouders mogen meehelpen. Als een kindje in zo'n kunstbaarmoeder zit, kan je dat n*iet.'

Tabel 2c: Positieve en negatieve effecten van het gebruik van de artificiële placenta op de zwangere of in het kader van de geboorte zoals benoemd door deelnemers aan de workshop op 7 april 2023

Positief	Negatief
ZWANGERE/GEBOORTE/PLACENTA	
	22. Magic bullets materialiseren niet[42,43]
	23. Maatschappelijke druk om alles te doen wat kan
	24. Gevolgen/rol voor zwangere - Lichamelijke integriteit moeder komt in het geding, door grotere druk om keizersnede te kiezen - Meer keizersneden met de gevolgen daarvan - Hoog risico keizersnede (gezien termijn wachten tot laatste moment)
	25. Moeder wordt gezien als kinderproducent
	26. Meer (mogelijk niet noodzakelijke) vroeggeboortes door medisch ingrijpen om te voorkomen dat het kind zich al klaar maakt voor de transitie van een geboorte.[44]
	27. Betere omgeving/omstandigheden voor de bevalling ("Bevallings beneficence")[45]
	28. Extra spannende bevalling
	29. Discussie over definities rondom geboorte, bijv. over wanneer het kind nu precies geboren is en daarmee ook over geboortedata en verjaardagen
	30. Effect op levensvatbaarheidsgrens en abortusgrens

Tabel 2d Positieve en negatieve effecten van het gebruik van de artificiële placenta op de zorg en het zorgpersoneel zoals benoemd door deelnemers aan de workshop op 7 april 2023

Positief	Negatief
ZORG/ZORGPERSONEEL	
	31. Het counselen en informeren van ouders wordt complexer. De omstandigheden zijn daarvoor ook niet goed: iemand is bijv. al aan het bevallen. Hoe verkrijg je dan geïnformeerde toestemming?
	32. Er ontstaat onduidelijkheid over wie (welk specialisme) welke verantwoordelijkheid heeft voor het kind[46]

42 '*De placenta, dat is echt mijn favoriete orgaan. Dat is zo een mooi, maar ook complex orgaan. Ik vraag me af of men ziet hoeveel ontzettend veel puntjes een placenta heeft. Dat is niet zomaar een paar canules en een beetje bloed en wat metabool en hormonen. Er zijn zoveel meer dingen die we niet weten.*'

43 *'Kan de placenta wel kunstmatig nagebootst worden? Is wel aan alles gedacht (maternaal/foeta*al?)'

44 *'Iatrogene vroeggeboorte door kind niet in transitie te laten k*omen'

45 *'Je kunt natuurlijk ook een bevallingsbeneficence, een optimalere omgeving voor de foetus cree*ren.'

46 De vraag kwam op of hiervoor eventueel een nieuw specialisme in het leven zou moeten worden geroepen.

Tabel 2d Continued

Positief	Negatief
ZORG/ZORGPERSONEEL	
33. Minder druk op de zorg - Andere manier van werken door zorgprofessionals (als het een zelfregulerend systeem is)	34. Meer druk op de zorg - Meer vereisten en verplichtingen - Andere manier van werking - Meer zorgpersoneel nodig
35. Meer innovatie, waardoor meer kennisvermeerdering en (mogelijke) verbetering van de huidige zorg voor en na de geboorte - Scholing nodig voor verdere ontwikkeling van zorgprofessionals	36, Meer innovatie, waardoor meer kennis nodig: - Scholing nodig voor verdere ontwikkeling van zorgprofessionals
	38. Slechter worden in het behandelen van kinderen van 28 – 29 weken
37. Besparing (zorg)kosten bv. door lange termijn zorg die bij betere uitkomsten niet meer nodig is	39. Toename (zorg)kosten door dure onderzoeken[47]
	40. Meer ligdagen in het ziekenhuis voor de pasgeborene
	41. Druk voor zorgverleners om te doen wat mogelijk is (voor bv. ouders)

Tabel 2e Positieve en negatieve effecten van het gebruik van de artificiële placenta op de zorg en het zorgpersoneel zoals benoemd door deelnemers aan de workshop op 7 april 2023

Positief	Negatief
TECHNIEK	
	42. De macht van bedrijven neemt toe: geld dat zij met de technologie kunnen verdienen verhoogt ook de druk om de technologie te gebruiken
43. Het is een glijdende schaal: wat eerst onwenselijk is/was, kan wenselijk worden door voortschrijdend inzicht en/of verdere ontwikkeling van de technologie - *'Voor jonger geboren kinderen kunnen zorgen kan ook positief zijn'*	44. Het is een glijdende schaal, waarbij de grenzen steeds verder zullen worden opgerekt', waarbij de techniek ook voor andere doeleinden wordt gebruikt[48,49]

47 Bijv. ten behoeve van het verder uitzoeken van de voor- en nadelen van de artificiële placenta en de verdere ontwikkeling en implementatie van de artificiële placenta.

48 *'Gaat dat ook niet weer betekenen, dat die grens daarvoor weer wordt opgerekt? Hoe is die grens? Vierentwintig weken? Ik denk dat er een tendens kan ontstaan dat men denkt: als ze dan al bij 24 weken in zo'n placenta kan komen, kan het misschien dan ook niet bij 20 weken? Dan kan het gaan schuiven.'*

49 *'Gaat het soms niet te ver? Is de wereld dan niet te maakbaar, waar is de grens?*

Tabel 2f Positieve en negatieve effecten van het gebruik van de artificiële placenta op de zorg en het zorgpersoneel zoals benoemd door deelnemers aan de workshop op 7 april 2023

Positief	Negatief
WETENSCHAPPELIJK ONDERZOEK	
	45. Als we eenmaal starten met wetenschappelijk onderzoek, dan is de vraag of we uiteindelijk nog kunnen beslissen dat de balans tussen de voor- en nadelen negatief uitvalt
	46. Bij deelname aan medisch-wetenschappelijk onderzoek naar de artificiële placenta kunnen deelnemers ten onrechte de indruk krijgen dat zij (en hun kind) persoonlijk voordeel kunnen hebben van het onderzoek[50]

Tabel 2g: Positieve en negatieve effecten van het gebruik van de artificiële placenta op de zorg en het zorgpersoneel zoals benoemd door deelnemers aan de workshop op 7 april 2023

Positief	Negatief
OVERIG	
	47. Meer data die beschermt moet worden[51,52]
	48. Deze nieuwe medisch-technologische mogelijkheid kan als sterk dwingend worden ervaren (het kan, dus het moet)[53]
	49. Proportionaliteit: geld dat hieraan wordt besteed, kan niet naar andere ontwikkelingen/ goede doelen, terwijl er al zoveel tekorten zijn in veel sectoren (bv. ouderenzorg)
	50. Toenemende ongelijkheid, waarbij de technologie niet voor iedereen beschikbaar is - Internationaal, bijv. in Afrika - Nationaal, niet voor iedere extreem te vroeggeborene (*'wie dan wel?'*)

Soms hadden deelnemers tegengestelde inschattingen van wat het effect zou kunnen zijn als te vroeg geboren kinderen in een artificiële placenta zouden worden geplaatst. Bijvoorbeeld welke invloed het kan hebben op de kwaliteit van leven van vroeggeboren kinderen. Sommige deelnemers gaven aan dat het de kwaliteit van leven van vroeggeboren kinderen zou kunnen verbeteren (effect 9). Andere deelnemers gaven aan dat gebruik van de artificiële placenta de kwaliteit van leven van vroeggeboren kinderen ook zou kunnen verslechteren (effect 10). Ook kwam het voor dat één en hetzelfde effect soms anders werd gewaardeerd.[54] Dit is bij bijvoorbeeld betere overlevingskansen (effect 11) en een overlevend kind is niet altijd goed (effect 12). Beide is hetzelfde effect, echter voor de ene deelnemer anders gewaardeerd dan voor de andere deelnemer.

50 Dit wordt ook wel de "therapeutische misconceptie" genoemd.

51 *'We gaan ontzettend veel data hebben van deze kinderen. We gaan het monitoren op een bepaalde manier. Hoe gaan we die data beschermen? Hoe gaan we daarmee om? Daar moeten we goed over nadenken.'*

52 '*Veel data, hoe gaan we die beschermen en hoe gaan we daarmee om? P*rivacy?'

53 Dit staat ook bekend als de "technologische imperatief" (imperatief betekent o.a. gebiedend en dwingend).

54 Als deelnemers rond hetzelfde onderwerp tegengestelde verwachtingen hadden van wat het effect zou zijn van het gebruik van de artificiële placenta, of als zij een effect anders waardeerden (als positief of als negatief), dan zijn deze effecten in de tabel direct naast elkaar gezet.

Waarden

De volgende stap in de Aanpak begeleidingsethiek is in kaart brengen welke waarden samenhangen met de eerder benoemde effecten. De werkwijze was daarbij als volgt:

- Deelnemers werden ingedeeld in 3 subgroepen die qua achtergrond zo divers mogelijk waren. Zo kwamen zij automatisch in gesprek met anderen met een verschillende achtergrond, met mogelijk een ander perspectief op het gebruik van de technologie.
- Daarna werd het totaal aantal benoemde effecten (zie de tabel in bijlage 2) door 3 gedeeld en werden de effecten evenredig verdeeld over de subgroepen. Elke subgroep ging dus met andere effecten aan de slag.
- Aan de subgroepen werd vervolgens gevraagd om uit het lijstje met effecten die aan hun subgroep waren toebedeeld een top-3 te maken van effecten die zij het belangrijkst vonden om aandacht aan te besteden.[55] Een selectie als deze wordt tijdens een workshop vooral om praktische redenen gemaakt. Het mogelijke gebruik van een technologie in een specifieke context is namelijk veelal te omvangrijk en complex om alles in 1 workshop te kunnen bespreken.[56]
- Doordat elke subgroep een top-3 maakte (steeds dus uit een ander lijstje met effecten), ontstond een selectie van 9 effecten die de deelnemers belangrijk vonden om *tijdens deze workshop* te bespreken.
- Voor één effect dat uiteindelijk uit het overzicht van effecten is verwijderd (omdat niet duidelijk was wat hiermee werd bedoeld), zijn door deelnemers enkele waarden benoemd. Dat zijn de waarden Gezonde ontwikkeling, hechting, kansengelijkheid en welzijn.[57]
- Tot slot heeft elke subgroep voor alle 9 effecten nagedacht over welke *waarden* een rol spelen bij deze effecten.

Tabel geeft een overzicht van de 9 effecten die door de 3 subgroepen als meest belangrijk werden gezien om aandacht aan te besteden (namelijk 2 positieve en 7 negatieve effecten), en welke waarden volgens de deelnemers een rol spelen bij deze effecten.

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55 In een enkel geval heeft een subgroep effecten samengevoegd om tot hun top-3 (voor het moment), dit staat aangegeven in tabel 3.

56 De selectie die ter plekke wordt gemaakt is daardoor niet automatisch ook een prioritering, in de zin dat aan sommige onderwerpen naderhand geen of minder aandacht zou hoeven worden besteed. In beginsel komen *alle* effecten en waarden die tijdens een workshop begeleidingsethiek worden benoemd in aanmerking om nader uitgewerkt en overwogen te worden.

57 Omdat een belangrijk doel van een workshop begeleidingsethiek is om zicht te krijgen op wat belangrijk is om te beschermen, zijn de bijbehorende waarden wel opgenomen in Tabel 4.

Tabel 3 Waarden die volgens de deelnemers een rol spelen bij een selectie van effecten die het ontwikkelen en het gebruik van de artificiële placenta zou kunnen hebben.

Effect	**Waarden (*alfabetisch*)**
3. Minder schade aan orgaansystemen (+) *Samengevoegd met:* 9. Betere kwaliteit van leven (+)	Autonomie, bescherming, gezondheid, kostenefficiëntie, kwaliteit van leven, ontwikkeling, participatie, plezier, recht op een open toekomst, veiligheid, verantwoordelijkheid,[58] welzijn
5. Onzekerheid/onbekendheid over uitkomsten, waardoor je een beslissing moet nemen zonder dit te kunnen baseren op bekende uitkomsten (-)	Autonomie, gezondheid, solidariteit, vrijheid, welzijn kind en ouder
8. Minder pijnlijke handelingen dan in de couveuse, zoals steeds prikken, waardoor er minder stress ontstaat voor de pasgeborene (+)	Bereiken maximale potentie, beschermen van je kind, gezondheid, integriteit lichaam, kwaliteit leven van ouders, kwaliteit van leven kind, verantwoordelijkheid, welzijn
13. Complexere keuzes voor ouders (-) - De techniek biedt hoop waar die nu misschien niet is, maar mogelijk brengt het aangrijpen van die hoop veel schade met zich mee. - Er ontstaat meer valse hoop	Verantwoordelijkheid, verbondenheid, zelfbeschikking
19. Niet/minder betrokken zijn bij de zorg voor je kind (-) - Effecten van het niet kunnen verzorgen - Het niet kunnen buidelen - Niet kunnen praten/zingen tegen je kind ('geen geluiden') - Minder mogelijkheden tot gezinsvorming (vergeleken met de huidige NICU behandeling) en de gevolgen daarvan voor imprint foetus	Binding/hechting, coping, functioneren, genegenheid, kunnen zorgen, relaties/contact, welzijn
24. Gevolgen/rol voor zwangere (-) - Lichamelijke integriteit moeder komt in het geding, door grotere druk om keizersnede te kiezen - Meer keizersneden met de gevolgen daarvan - Hoog risico keizersnede (gezien termijn wachten tot laatste moment)	Goed ouderschap, lichamelijke integriteit, welzijn zwangere, zelfbeschikking
48. Deze nieuwe medisch-technologische mogelijkheid kan als sterk dwingend worden ervaren (het kan, dus het moet)	Geduld, weerbaarheid, reproductieve autonomie, welzijn, zorgvuldigheid
49. Proportionaliteit: geld dat hieraan wordt besteed, kan niet naar andere ontwikkelingen/goede doelen, terwijl er al zoveel tekorten zijn in veel sectoren (bv. ouderenzorg)	Fairness, proportionaliteit, toegankelijkheid, zinvolheid, zuinigheid (*frugalty*)

58 'Verantwoordelijkheidsgevoel' is verkort tot 'verantwoordelijkheid'

In totaal werden door de deelnemers 35 waarden benoemd. Zonder uitzondering kwamen bij één en hetzelfde effect steeds meerdere waarden aan bod. Dat is van belang omdat het uitdrukt dat bij effecten die een technologie kan hebben steeds meerdere zaken in het spel zijn die we waardevol vinden. Het betekent ook dat bij elke poging om gewenste effecten te bevorderen en bij elk poging om ongewenste effecten te beperken of te voorkomen, steeds meerdere zaken in het spel zijn die we waardevol vinden. Kortgezegd: bij elke handelingsoptie zijn altijd meerdere waarden in het spel.

In *Tabel 4* worden de waarden nog eens apart genoemd (alfabetisch).

Tabel 4: Waarden die aan bod zijn gekomen tijdens de workshop van 7 april (alfabetisch)

Waarden		
Autonomie / Zelfbeschikking	Kostenefficiëntie	Toegankelijkheid
Bereiken maximale potentie	Kunnen zorgen	Veiligheid
Beschermen (van je kind)	Kwaliteit van leven (ouders, kind)	Verantwoordelijkheid(sgevoel)
Binding/hechting	Lichamelijke integriteit	Verbondenheid
Coping	Weerbaarheid	Vrijheid
Fairness	Ontwikkeling	Welzijn (kind, ouder, zwangere)
Functioneren	Participatie	Zinvolheid
Geduld	Plezier	Zorgvuldigheid
Genegenheid	Proportionaliteit	Zuinigheid (*frugalty*)
Gezonde ontwikkeling	(Recht op) een open toekomst	
Gezondheid	Relaties/contact	
Goed ouderschap	Reproductieve autonomie	
Kansengelijkheid	Solidariteit	

Sommige waarden werden door (verschillende) deelnemers in (ongeveer) dezelfde bewoordingen bij meerdere effecten genoemd. Tabel 5 geeft hiervan een overzicht.

Tabel 5 Waarden die door de deelnemers bij meerdere effecten werden genoemd (in dezelfde bewoordingen)

Waarden die door de deelnemers bij meerdere effecten werden genoemd
Autonomie/ zelfbeschikking (3+9, 5, 24, 36)
Bescherming (3+9, 8)
Gezondheid (3+9, 5)
Kwaliteit van leven (3+9, 8)
Lichamelijke integriteit (19, 24)
Verantwoordelijkheid (3+9, 8, 36)
Welzijn (3+9, 8, 19, 24, 46)

Ook dit is van belang. Het geeft aan dat zaken die we waardevol vinden op verschillende manieren kunnen worden beïnvloed: positief en negatief, maar daarbinnen ook op verschillende manieren. In *Tekstbox 2* wordt een voorbeeld gegeven van positieve en negatieve effecten die gebruik van de artificiële placenta als behandeling bij extreme vroeggeboorte volgens de deelnemers kan hebben op de waarden autonomie en zelfbeschikking.

Tekstbox 2 Positieve en negatieve effecten die gebruik van de artificiële placenta als behandeling bij vroeggeboorte volgens de deelnemers kan hebben op autonomie/ zelfbeschikking

Bij het benoemen van effecten die gebruik van de artificiële placenta als behandeling bij extreme vroeggeboorte zou kunnen hebben en welke waarden daarbij een rol spelen, brachten de deelnemers de waarden autonomie en zelfbeschikking in verband met 1 *positief* effect (effect 3+9) en met 3 *negatieve* effecten (effecten 5, 24 en 36).

Als positief effect werd genoemd dat gebruik van de artificiële placenta tot een betere kwaliteit van leven kan leiden. De kwaliteit van leven van het kind zou kunnen verbeteren als door gebruik van de artificiële placenta minder schade aan orgaansystemen optreedt en als vroeggeboorte minder negatieve effecten heeft en gepaard gaat met minder morbiditeit (vergeleken met de huidige situatie en behandeling).

Dit zou op twee manieren kunnen bijdragen aan autonomie en zelfbeschikking. Ten eerste zou het de autonomie of zelfbeschikking van de aanstaande *ouders* kunnen versterken door hen de mogelijkheid te bieden om te kiezen voor een behandeling die de kwaliteit van leven van hun kind kan verbeteren ten opzichte van wat er zonder die behandeling zou kunnen gebeuren. Ten tweede zou een bepaalde mate van kwaliteit van leven de autonomie van het *kind* kunnen versterken. Bijvoorbeeld als de betere kwaliteit van leven die het resultaat is (/kan zijn) van het gebruik van de artificiële placenta, bijdraagt aan een (meer) open toekomst voor het kind.

Volgens de deelnemers zou gebruik van de artificiële placenta als behandeling bij extreme vroeggeboorte autonomie of zelfbeschikking ook *negatief* kunnen beïnvloeden. In dit verband werden genoemd:

- Onzekerheid/onbekendheid over uitkomsten (effect 5);[59]
- Mogelijke druk om voor een keizersnede te kiezen, en daaraan gekoppeld de lichamelijke integriteit van de zwangere en het beeld van de moeder als 'kinderproducent' (effect 24); en
- De technologische imperatief ('het kan, dus het moet': effect 46).

Wat deze effecten gemeen hebben is dat ze in verband werden gebracht met een nadelig effect op autonomie en zelfbeschikking. Er zijn ook belangrijke verschillen. Die verschillen hebben te maken met de *opzichten waarin* autonomie of zelfbeschikking onder druk kan komen te staan:

- Door *druk op betrokkenen* om een bepaalde keuze te maken: om de artificiële placenta te gebruiken omdat het kan (effect 46), om een keizersnede te laten doen (effect 24);
- Door *gebrek aan informatie* bij het maken van keuzes: onzekerheid/onbekendheid over uitkomsten (effect 5); en
- Als de moeder uitsluitend als middel zou worden beschouwd (als 'kinderproducent') en niet meer als "doel op zich" (een uiterste invulling van effect 24).

De korte bespreking in *Tekstbox 2* maakt duidelijk dat gebruik van een technologie een waarde zoals autonomie tegelijkertijd kan bevorderen (effect 3+9) en een bedreiging voor die waarde kan vormen (effecten 75, 24, 36). Bij het trekken van conclusies over of en zo ja hoe gebruik van een technologie een waarde kan helpen bevorderen, of daar een bedreiging voor kan vormen, is dus van belang om duidelijk te maken: a) hoe de betreffende waarde wordt opgevat; en b) of alle relevante opzichten waarin de waarde kan worden beïnvloed, in ogenschouw zijn genomen.

59 Effect 3 (positief) en effect 7 (negatief) zijn sterk met elkaar verbonden. Bij effect 3 is de gedachte dat gebruik van de artificiële placenta als behandeling bij extreme vroeggeboorte de kwaliteit van leven van het kind kan verbeteren. Maar bij effect 7 wordt benadrukt dat er vooralsnog sprake is van onzekerheid/ onbekendheid over uitkomsten.

Vervolgstappen

Zoals gezegd is er om praktische redenen tijdens de workshop voor gekozen om op een selectie van effecten te focussen. En om voor die effecten in kaart te brengen welke waarden volgens de deelnemers een rol spelen bij die effecten. Om een completer beeld te krijgen van ethische aspecten van het gebruik van de artificiële placenta zou in vervolgstappen ook aandacht kunnen worden besteed aan het benoemen van waarden voor alle *overige* effecten die in kaart zijn gebracht.

Fase 3: Handelingsopties

Nadat de technologie in context is besproken (fase 1) en deelnemers in een dialoog actoren, effecten en waarden hebben benoemd (fase 2), wordt in fase 3 in kaart gebracht wat concreet gedaan kan worden om positieve effecten te bevorderen en negatieve effecten zoveel mogelijk te voorkomen. Door zo over handelingsopties na te denken, kunnen belangrijke waarden zo goed mogelijk worden beschermd. Anders gezegd, het biedt ons de gelegenheid om waarden die we belangrijk vinden tot uitdrukking te brengen in wat we doen (en laten). Zo kan stap voor stap een beeld worden gevormd of de artificiële placenta zo toegepast kan worden dat waarden die in de geboortezorg belangrijk zijn, er (voldoende) mee tot uitdrukking kunnen worden gebracht.

Er werd een korte uitleg gegeven over de verschillende 'niveaus' waarop over verantwoorde handelingsopties met betrekking tot het gebruik van de artificiële placenta als behandeling bij extreme vroeggeboorte kan worden nagedacht. Het kan bijvoorbeeld gaan over het ontwerp van de **technologie**, het aanpassen van de (fysieke, sociale of institutionele) **omgeving** waarbinnen de artificiële placenta ingezet zou worden en het gedrag van mensen (**gebruik**). De deelnemers gingen vervolgens in subgroepen aan de slag om handelingsopties te bedenken voor de positieve en negatieve effecten uit Tabel 6a tot en met 6i geeft hiervan een overzicht.

Tabel 6a: Handelingsopties bij effect 'Effecten van omgeving artificiële placenta op kind' die werden genoemd in de workshop

Handelingsopties			
Effect	**Technologie**	**Omgeving**	**Gebruiker**
Effecten van omgeving artificiële placenta op kind (-)	· De mogelijkheid om de hartslag af te spelen van ouders in de artificiële placenta · De mogelijk maken dat ouders hun handen op de artificiële placenta kunnen leggen · Kind kunnen zien terwijl het in de artificiële placenta zit (door de artificiële placenta transparant te maken, of m.b.v. camera's) · De mogelijkheid om de artificiële af te dekken met een doek, de rust voor het kind garanderen · Darm-/stemgeluid mogelijk van ouders kunnen afspelen in de artificiële placenta · Mogelijkheid creëren om direct tegen het kind te kunnen praten[60] · Beweging van het kind kunnen terugkoppelen naar ouders (sensoren) · Vriendelijk design (zachte kleuren, ronde vormen, niet koud, kleur-materiaal)[61] · Het dag-nacht-ritme nabootsen · Beweging moeder nabootsen		

60 *'Het lijkt me fijn als je direct kan praten tegen je kind en niet dat daar iets kunstmatigs wordt ontwikkeld, maar dat het echt eigen oudergeluiden zijn. Niet de stem van iemand anders die op een bandje wordt gezet.'*

61 *'Hoe het er uitziet qua vormen. Ronde vormen. Dat er dat er een soort rondheid in zit, niet koud en hoekig als een aquarium.'*

Tabel 6b Handelingsopties bij effect 3 & 9 die werden genoemd in de workshop

Handelingsopties			
Effect	**Technologie**	**Omgeving**	**Gebruiker**
3. Minder schade aan orgaansystemen (+) *Samengevoegd met:* 9. Betere kwaliteit van leven (+)	· Goede balans in de antistolling garanderen · Behoud van foetale fysiologie · Goede afstelling van Totale Parenterale Voeding (TPV) · Adequate monitoring van vitale waarden garanderen · Voorkomen van contact met kamerlucht/ waarborgen dat het kind "onder water" blijft · Systemen ontwikkelen die 'alle' data veilig kunnen opslaan en clinical support kunnen bieden	· Verzekering inlichten optie	· Cannulatietraining[62]: snel, vaardig, dedicated team. · Belang van objectief onderzoek wat gedaan dient te worden duidelijk maken bij ontwikkelaars en wetenschappelijke wereld[63]

Tabel 6c Handelingsopties bij effect 5 die werden genoemd in de workshop

Handelingsopties			
Effect	**Technologie**	**Omgeving**	**Gebruiker**
5. Onzekerheid/ onbekendheid over uitkomsten, waardoor je een beslissing moet nemen zonder dit te kunnen baseren op bekende uitkomsten (-)	· Door ontwikkelen van de techniek o.b.v. tussentijdse resultaten (evaluatiemomenten inbouwen)	· Grenzen stellen bij ontwikkeling van onderzoek over inclusie en exclusiecriteria voor kind en vrouw, goede stopcriteria formuleren · Verzekeren lange termijn follow-up van geïncludeerde deelnemers, evaluatie van deze resultaten voordat onderzoek door kan gaat met volgende fase, brede follow-up op verschillende gebieden · Transparantie en 'eerlijke data', dus niet mooier voordoen ten behoeve van ontwikkeling van technologie, dan dat het is. · Keuzen inzichtelijk/ overzichtelijk maken, tijdig delen en transparant zijn	

62 Cannulatie betekent dat er canules (plastic slang) worden ingebracht waardoor het bloed het lichaam in en uit gaat. Bij cannulatietraining wordt de procedure van cannulatie getraind .

63 *'Cruciaal voor het [effect 'Minder schade aan orgaansystemen'] is: dat moet gewoon op een goede, objectieve manier onderzocht worden'*

Tabel 6d Handelingsopties bij effect 8 die werden genoemd in de workshop

Handelingsopties			
Effect	**Technologie**	**Omgeving**	**Gebruiker**
8. Minder pijnlijke handelingen dan in de couveuse, zoals steeds prikken, waardoor er minder stress ontstaat voor de pasgeborene (+)	· Garanderen dat systeem genoeg bloed heeft voor labbepalingen · Neo comfort score in 'techniek' ontwikkelen en monitoren		

Tabel 6e Handelingsopties bij effect 19 die werden genoemd in de workshop

Handelingsopties			
Effect	**Technologie**	**Omgeving**	**Gebruiker**
19. Niet/minder betrokken zijn bij de zorg voor je kind (-) - Effecten van het niet kunnen verzorgen - Het niet kunnen buidelen - Niet kunnen praten/ zingen tegen je kind ('geen geluiden') - Minder mogelijkheden tot gezinsvorming (vergeleken met de huidige NICU behandeling) en de gevolgen daarvan voor imprint foetus	· Hartslag van ouders afspelen in de artificiële placenta · Mogelijk maken dat ouders hun handen op de artificiële placenta kunnen leggen · Kind kunnen zien terwijl het in de artificiële placenta zit (door de artificiële placenta transparant te maken, of m.b.v. camera's) · Afdekken met doek over de artificiële placenta, rust voor kind garanderen · Darm/stemgeluid van ouders mogelijk kunnen afspelen · Mogelijk maken om direct tegen kind te kunnen praten · Mogelijkheid dat de bewegingen die het kind maakt terug te kunnen koppelen naar ouders (sensoren) · Vriendelijk design maken (zachte kleuren, ronde vormen, niet koud, kleur-materiaal) · Dag-nacht nabootsen · Beweging moeder nabootsen	· Onafhankelijke begeleiding/counseling · Compassie van zorgverleners	· Zorgverleners moeten pro-actief zijn in het betrekken van ouders in wat zij wel kunnen doen in de zorg van hun kind in de artificiële placenta en qua aanrakingen.[64]

64 *'Dan zou je het kunnen stimuleren vanuit de zorgverleners, dat ouders misschien thuis gesprekjes of muziekjes opnemen voor hun kind. Dat je dat stimuleert als zorgverlener en dat ouders dat mee kunnen geven en af kunnen spelen. Dat je dus niet alleen de verantwoordelijkheid bij de ouders legt, maar dat je ook als zorgverleners dat stimuleert.'*

Tabel 6f Handelingsopties bij effect 24 die werden genoemd in de workshop

Handelingsopties			
Effect	**Technologie**	**Omgeving**	**Gebruiker**
24. Gevolgen/rol voor zwangere (-) - Lichamelijke integriteit moeder komt in het geding, door grotere druk om keizersnede te kiezen - Meer keizersneden met de gevolgen daarvan - Hoog risico keizersnede (gezien termijn wachten tot laatste moment)	· Keuzehulp ondersteuning: keuzehulp moet helpen in het personaliseren van beslissingen met respect voor alle keuzes, visueel en met woorden. Aanpassen aan doelgroep en in verschillende talen. · Informatie geven over vaginaal vs. sectio, specifiek gericht op de moeder · Techniek geschikt maken voor vaginale partus en voor tweelingen.	· Genoeg tijd hebben om te beslissen · Alleen voor ouders die op tijd zijn geïnformeerd over deze mogelijke behandeloptie en de onzekerheid die dit met zich meebrengt · De zwangere vanaf begin van opname direct inlichten over deze mogelijkheid · Goede keuzehulp voor deze behandeloptie met alle voor- en nadelen en transparantie over wat het inhoudt · Onafhankelijke begeleiding/counseling door onderzoeker/arts · Compassie van zorgverleners	· Er moet eerlijke counselling gegarandeerd worden over het onderzoeksdoel en de behandeling

Tabel 6g Handelingsopties bij effect 36 die werden genoemd in de workshop

Handelingsopties			
Effect	**Technologie**	**Omgeving**	**Gebruiker**
13. Complexere keuzes voor ouders (-) - De techniek biedt hoop waar die nu misschien niet is, maar mogelijk brengt het aangrijpen van die hoop veel schade met zich mee. - Er ontstaat meer valse hoop	· Keuzehulp ontwikkelen, met visuele ondersteuning → Echte foto's (niet alleen schematisch van baby's en techniek) → Expansie opties dus meer-minder detail op verzoek · Multimedia voor keuzehulp (papier/boek/site) te kiezen door ouders	· Ouders genoeg tijd geven om te beslissen · Met name tijdens first in human trials, alleen aanbieden aan ouders die dit op tijd weten zodat zij hier wel overwogen over kunnen nadenken · Zwangere vanaf het begin inlichten over deze behandeloptie · Goede keuzehulp voor deze behandeloptie met alle informatie en voor en nadelen	

Tabel 6h Handelingsopties bij effect 46 die werden genoemd in de workshop

Handelingsopties			
Effect	**Technologie**	**Omgeving**	**Gebruiker**
48. Deze nieuwe medisch-technologische mogelijkheid kan als sterk dwingend worden ervaren (het kan, dus het moet)	· Keuzehulp ondersteuning: keuzehulp moet helpen in het personaliseren van beslissingen met respect voor alle keuzes, visueel en met woorden. Aanpassen aan doelgroep en in verschillende talen. · Informatie geven over vaginaal vs. sectio, specifiek gericht op de moeder	· Transparantie over resultaten van onderzoeken die naar de techniek worden gedaan, volledige openheid over resultaten dus ook tegenvallende resultaten.	

Tabel 6i: Handelingsopties bij effect 47 die werden genoemd in de workshop

Handelingsopties			
Effect	**Technologie**	**Omgeving**	**Gebruiker**
49. Proportionaliteit: geld dat hieraan wordt besteed, kan niet naar andere ontwikkelingen/ goede doelen, terwijl er al zoveel tekorten zijn in veel sectoren (bv. ouderenzorg)	· Stoppen met de ontwikkeling · Goedkopere materialen gebruiken · Zorgen dat het ook naar andere gebieden getransporteerd kan worden	· Grenzen stellen aan financiële input · Goede berekeningen/ kosten-baten analyse · Verzekeren internationale samenwerkingsverbanden · Betrekken zorgverzekeraars in de ontwikkeling van de techniek	

Tabel 6a tot en met 6i laten zien dat deelnemers voor vrijwel alle mogelijke effecten meerdere typen handelingsopties hebben bedacht, bijvoorbeeld een combinatie van technologische opties, opties in de (fysieke, sociale of institutionele) omgeving waarin de technologie wordt gebruikt en opties die te maken hebben met het gedrag of vaardigheden van de gebruiker van de technologie. Uitzonderingen zijn het effect van omgeving artificiële placenta op het kind en effect 19 (Minder pijnlijke handelingen dan in de couveuse, zoals steeds prikken, minder stress voor de pasgeborene). Voor deze effecten hebben de deelnemers handelingsopties in de categorie technologie benoemd, niet in de categorie omgeving en gebruiker.

Het is mogelijk dat niet voor elk effect dat je zou willen bevorderen (de positieve effecten) of juist zou willen beperken of voorkomen (de negatieve effecten), in elke categorie een handelingsoptie beschikbaar is. Tegelijk is denkbaar dat bij effecten waarvoor nog niet in elke categorie een handelingsoptie is benoemd, nog handelingsopties bedacht zouden kunnen worden. Voor de handelingsopties geldt dus hetzelfde als wat eerder over de lijst met actoren (*Tabel 1*), de lijst met effecten en de lijst met waarden (*Tabel 3 t/m 5*) werd gezegd: het overzicht is mogelijk (en vermoedelijk) niet volledig. Het is een basis om op verder te bouwen. Zo kunnen bijvoorbeeld ook nog handelingsopties worden bedacht voor de overige effecten die in kaart zijn gebracht.

Terugblik en afronding

Aan het einde van de workshop is teruggekeken en besproken wat de Aanpak begeleidingsethiek concreet heeft opgeleverd. De deelnemers gaven aan dat het veel nieuwe inzichten oplevert en dat er in korte tijd gedurende de workshop veel besproken is. Daarnaast werd de aanwezigheid van een brede groep van deelnemers ieder met hun eigen achtergrond als meerwaarde ervaren.

Ouders gaven aan dat ze het een veilige omgeving vonden en daardoor het gevoel hadden alles te kunnen zeggen. Zij waardeerden het erg dat hun input serieus wordt genomen en wordt meegenomen in de ontwikkeling van deze technologie.

Aan het einde van de workshop is o.a. besproken wat deelnemers meenemen uit de workshop en of de verwachtingen waarmee zij naar de workshop waren gekomen, uitgekomen zijn.

Zoals één van de deelnemers duidelijk benoemd:

'*Ik vond het boeiend, omdat ik allemaal nieuwe dingen hoorde die zo essentieel zijn. Het gaat toch uiteindelijk waarschijnlijk wel komen ergens, maar het voelt alsof we er invloed op zouden kunnen hebben door mee te denken. Als wij dat niet doen, wie gaat het dan wel doen?*'

Chapter 7

Stakeholder perspectives on the design of first-in-human trials for artificial amnion and placenta technology: a qualitative study

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Abstract

Objective: Artificial Amnion and Placenta Technology (AAPT), designed to improve outcomes in extreme prematurity, has shown promise in animal studies, with human trials anticipated soon. This study seeks to inform the responsible design of future trials by utilizing insights from parents who experienced an (imminent) extremely premature birth and perinatal healthcare professionals (HCPs).

Design: A qualitative study using individual and focus group interviews.

Setting: This study was part of a Dutch study called Toward Individualized care of the Youngest.

Sample: Fifteen parents who experienced an (imminent) extremely premature birth and 46 HCPs were interviewed.

Methods: Eight focus-group and five individual interviews were performed and transcribed. The transcripts were thematically analysed.

Main outcomes and measures: The perspectives of HCPs and experienced parents on what they considered essential for human AAPT trials.

Results: Analyses revealed some critical considerations represented in six themes: (1) optimise the animal model, (2) determine the goal of human trials, (3) carefully establish the research population, (4) formulate stop criteria, success criteria and outcome measures, (5) determine the role for parents during the AAPT trial, and (6) develop protocols for the trial and address logistical considerations.

Conclusion: This study emphasizes the critical role of stakeholder involvement in safeguarding the responsible design of human AAPT trials. Defining the trial objectives including well-defined stop criteria and follow-up schemes is a key element for the human AAPT trials. Establishing consensus among stakeholders is essential, as shared recommendations will facilitate alignment of expectations and promotes engagement.

Introduction

Worldwide, the main cause of perinatal mortality and morbidity is extremely premature birth, defined as birth before 28 weeks of gestation.[1] Extremely premature born neonates are at risk of mortality and serious physical, mental and social problems caused by the far-too-early transition from maternal-placental life support to extra-uterine life.[2] Additionally, although the offered specialized intensive care treatment after birth is crucial for survival, it can also lead to health complications, including additional iatrogenic damage, such as in bronchopulmonary disease (BPD). In light of these risks, recent research has studied techniques to postpone the transition to extra uterine physiology, such as the artificial amnion and placenta technology (AAPT).[3,4] Generally, AAPT technologies aim to improve clinical outcomes by limiting complications, increasing survival rates and improving quality of life for extremely premature infants.[3-5] Various models of the AAPT using lambs and piglets have been studied showing promising results.[3,4,6] First in-human trials of the technology are expected in the coming years.[7]

Designing human trials for the AAPT presents complex ethical, clinical, and logistical challenges. There is no consensus in literature on how to conduct these human trials.[8] Key considerations include patient selection criteria, ethical issues in research methods such as randomization in neonatal trials, and strategies to mitigate the risks associated with experimental technologies.[8,9] While existing AAPT-research primarily focuses on pre-clinical technique development[5,10], animal study challenges and outcomes[4-6,10], and conceptual ethical and legal considerations[9,11-14], studies addressing the design of human trials for AAPT are limited.[9,11,15] Moreover, research incorporating the perspectives of direct stakeholders on this topic is notably absent. This study aims to fill this gap by utilizing insights and experiences of parents who experienced an imminent or actual extreme premature birth and of healthcare professionals (HCPs) involved in perinatal care for extremely premature infants to guide the responsible design for the human AAPT trials.

Methods

This research is part of the Dutch study Toward INdividualized care for the Youngest (TINY), focusing on complex decision-making in extreme prematurity.[16-19] TINY-3 focuses on the AAPT as potential treatment for extreme prematurity. A detailed description of the method is provided in *Supplemental files TINY-3, file 1.* The process of the TINY-3 study with different phases is also displayed in *figure 1* in *Supplemental files TINY-3, file 2*. This mixed method approach was conducted to adhere to participants' preferences and to ensure thematic saturation. The first phase consisted of a stakeholders meeting following a guidance ethics approach (*intermezzo C*).[20,21] To further explore and expand on the main results of the stakeholders meeting, we conducted semi-structured focus group interviews and individual interviews (phase 2). For phase 2, inclusion criteria for participants were (1) parents who experienced an imminent or actual premature birth before 28 weeks gestation

(henceforth: parents) and (2) HCPs in perinatal care. Parents were recruited through the TINY-database. First, a general email was sent to all parents listed in the database, inviting them to participate in the study. Based on the responses, we then reached out to additional parents with diverse experiences of preterm birth and personal backgrounds to ensure a broad range of perspectives and a representative population. This article presents the TINY-3 results on relevant considerations of parents and HCPs to safeguard the responsible design of future human AAPT trials. Both perspectives are essential because the HCPs will be the ones responsible for the care of these children, and the families would be the main characters in the trials.

One interview guide was developed for both groups based on the stakeholders meeting and the expertise of our multidisciplinary team (*Supplemental files TINY-3, file 3*). Six focus group interviews with HCPs (n=46) and two focus group interviews with parents (n=13) were conducted, as well as five individual interviews with parents (n=5). The HCPs represented various specialties, and parents had different experiences with extreme premature birth. All interviews started with an explanation of the AAPT and the Dutch context, as summarized in box 1. The starting point was the current status of the AAPT development with the focus on the potential upcoming human AAPT trials - rather than possible future applications or clinical implementations. During the interviews, conceptual AAPT-prototypes developed by the Dutch Perinatal Life Support-consortium were presented to provide participants with a more tangible understanding of the technology's potential design and functionalities. Data analysis involved thematic content analysis independently performed by researchers (AB, RK) following Braun and Clarke's guidelines. This included familiarizing ourselves with the data, generating initial codes, searching for themes based on these codes, reviewing the themes, defining and naming the themes, and writing the manuscript.[22]

Box 1: The Dutch context and the Artificial Placenta

In the Netherlands, the period between 24 and 26 weeks gestation is considered the gray zone, permitting both intensive care treatment and palliative care. For infants born before 24 estimated weeks gestation, palliative care is the standard approach, while those born after 26 weeks typically receive intensive care treatment. These prognosis of these infants born at the limit of viability is uncertain.

Currently, a number of research groups worldwide are working on a new technology as treatment for this group of infants, called the AAPT. Until now, only animal research has been conducted, with notable success in allowing lambs to grow in an AAPT for four weeks by Flake et al in Philadelphia.(1, 2) The technology aims to mimic the function of the amniotic sac, amniotic fluid and placenta. To facilitate the transition from the mother to the artificial placenta, it is essential to prevent the fetus from beginning to breathe at birth. A cesarean section appears to be necessary to ensure the success of this process. In this fluid-filled environment of the AAPT, the infant is fitted with cannulas (large infusion tubes) connected to the artificial placenta. After the transition from the mother to the artificial placenta, the infant receives oxygen and nutrients through these cannulas. Continuous medication to thin the blood will be required, as well as ongoing monitoring of heart rate, oxygen supply, brain, and muscle activity.

In the Dutch context, it is currently suggested that the child can be treated in the AAPT for a duration of 28 days. This implies that at a gestational age of 28 weeks, further treatment will continue in an incubator, similar to current NICU care. At this stage, the infant will be removed from the AAPT. The AAPT is intended to support infants born at the current threshold of around 24 weeks, as suggested by the Dutch Perinatal Life Support-consortium. Following four-week testing on lambs and favorable Neonatal Intensive Care Unit (NICU)-outcomes for infants >28 weeks, the envisioned treatment would extend until 28 weeks gestation.

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Results

Demographic information of the participants is presented in Table 1A and 1B (*Supplemental files TINY-3, file 4*). Results are represented in six themes derived from the data, representing the perspectives of both parents and HCPs on considerations for the upcoming human AAPT trials namely: (1) optimize the animal model, (2) determine the goal of the first in-human trials, (3) carefully establish the research population, (4) formulate stop criteria, cut-off points, and outcome measures, (5) determine the role for parents during the AAPT trials, and (6) develop protocols for the trial and address logistical challenges. The themes are presented in a stepwise order reflecting what should be addressed first before moving to the next phase and are supported by quotes of parents and HCPs extracted from the interviews. For each quote, it is specified whether it was stated by a HCP or a parent, along with the corresponding interview number. Additionally, supplementary quotes are provided in Table 2 to further support the findings.

1. Optimize the animal model

One of the main concerns expressed by parents and HCPs was the reliability of animal research results for informing subsequent steps in human trials. They agreed that proceeding to human AAPT trials at this moment would be *"going too fast"* and emphasized the need

to conduct more animal testing: "*maybe you should optimize your animal model a bit more before exposing it to others"* [HCP, F1].

The current animal models were deemed insufficient because they do not accurately reflect human pregnancy or fetal maturation. The lamb fetuses matured to full term in the AAPT, making parents and HCPs worried about how potential risks and consequences could be accurately studied. As one HCP stated: "*we need to have sufficient research results to make a comparison in terms of maturity. This would allow us to say more than just: it is technically possible*" [HCP, F2]. Furthermore, they stressed the importance of collecting data about the lambs over a longer period to collect potential long-term effects. One parent suggested: "*maybe those little lambs should roam around in the meadow for a few years*" [Parent, I3].

2. Determine the objective of first in-human trials

Particularly HCPs emphasized the importance of establishing the scientific objective before proceeding to human AAPT trials, linking it to other requirements and criteria such as establishing the research population (see theme 3) and defining outcome measures (see theme 4). During the interviews, potential goals emerged. Parents stated that the objective should be to test "*if the technology works*"[and did not specify what parameters would include successful functioning of the technology. HCPs framed the trials as safety trials and discussed that the aim should be "*data collection of benefits, harms and side effects*" [HCP, F4]. All considered it crucial to ensure the objective of the human AAPT trials in order to gather data that is meaningful for the future population that would be treated in the AAPT.

3. Carefully establish the research population

Participants stressed the need to carefully define the group of patients (mothers and infants) that would constitute the research population. Broadly, the following groups were considered eligible by HCPs: (i) based on maternal and placental factors, (ii) based on the infant's prognosis with either favorable or critical prognoses, or (iii) based on gestational age and the limit of viability.

The following groups were suggested by parents: (i) based on gestational age with "*minimal chances of survival*" or to explore *"interventions before 24 weeks of gestation*", (ii) based on social factors, preferring parents who already had a child to avoid "*potential complications from a cesarean section that could affect future fertility"*, or (iii) based on the level of urgency of the extremely premature birth.

No consensus was reached on which cohort would be most suitable for the AAPT trials. However, HCPs suggested to personalize the decision on whether the AAPT would be a suitable option for both the parents and the infant on a case-by-case basis. Furthermore, the discussions tended more towards indications of the infants instead of maternal indications, supported by arguments on various levels; HCPs were mostly focused on the

medical substantive arguments and parents reasoned from a broader context based on their experience with extreme premature birth.

The HCPs mentioned that the cohort that is the most ethically justifiable – e.g., non-viable infants – to involve in AAPT trials would produce the weakest research outcomes, methodologically speaking, and vice versa. "*Infants [born after placental insufficiency] often have poorer outcomes compared to their peers. [...] As a result, early experiments could yield poor outcomes, which might not be attributable to the method itself but rather to the characteristics of the infants involved*" [HCP, F2]. Lastly, HCPs worried about the selection bias that would occur with each cohort you would choose for the human trial.

4. Formulate stop criteria, success criteria and outcome measures

Parents and HCPs agreed that outcome measures should be carefully formulated before trials with the AAPT start. Both groups agreed that survival should not be the only outcome measure, as it would provide a one-sided view of the technology, and emphasized the need to examine long-term outcomes for the infant, as well as the impact on parent-child bonding. One HCP stated: "*This experiment only ends, as far as I'm concerned, once the long-term effects have been established*" [HCP, F1]. Other outcome measures suggested by HCPs were intraventricular hemorrhage, infections, long-term outcomes for parents in terms of mental health and bonding with their child and unspecified long-term outcomes for the siblings.

HCPs discussed that stop criteria and success criteria should also be formulated beforehand. Criteria for stopping the trial should be established, addressing when the trial itself should be stopped and when an individual treatment within the AAPT trials should be discontinued and switched to treatment at the Neonatal Intensive Care Unit (NICU). Additionally, they argued that success criteria should be defined to determine when AAPT treatment could be deemed superior to the current NICU-treatment.

5. Determine the role for parents during the trial with the AAPT

Parents and HCPs stated that the autonomy of parents should be ensured during the AAPT trials by actively involving them in their infant's care. Parents argued that they should be prepared for the sight of their child in an AAPT and should be told what is expected from them, since they would not be able "*to hold them*", "*change the diaper*", or "*to care for them*" [Parents, F7 and F8]. HCPs worried how the trials would affect parents, because parents have a significant role in current NICU-care which also improves the bonding with their infant. One HCP stated: "*I think parents are a precondition [in how to design the trails with AAPT]"* [HCP, F2].

6. Develop protocols for the trial & address logistical considerations

Parents and HCPs expressed the need for protocols, safety procedures and addressing logistical considerations regarding AAPT trials. HCPs mostly stressed the importance of protocols for crucial moments like the transfer from the uterus to the AAPT or in case

of an emergency. As one HCP stated: "*We need to become technically flawless in [technical procedures]. That is an absolute requirement for me*" [HCP, F2]. Protocols and guidelines should also be developed for situations in which the transfer fails, the infant's condition in the AAPT declines or dies in the AAPT. For the first two situations, participants suggested the experiment to be stopped and treatment to be converted to standard care: "*It seems very important to me, as a parent, to know that [...] if we see that things are deteriorating, we stop immediately and take other measures*" [Parent, F7].

Finally, the centralization of AAPT-care was discussed. Particularly in the context of the trials, parents and HCPs envisioned this treatment being available exclusively at a single center as it would allow for better control of the environment, and concentration of expertise in one location. Another suggestion was to facilitate the transport of patients using the AAPT between hospitals.

7. *Overall trends*

The identified themes represent overarching topics that are relevant to both HCPs and parents showing both similarities and differences between the groups. Data collected from HCPs was observed to be noticeably richer and more detailed than that from parents. Observations indicated that participants' assumptions, interpretations, or misconceptions regarding the AAPT may have shaped the findings. Although the starting point for discussion was the context of potential human trials, participants often took a broader perspective, not consistently distinguishing between the trial context and the AAPT potential future role in care. This highlights the importance of considering care-related concerns, which could be included as an outcome measure in future trials. Finally, a clear interconnection between the identified themes emerged, with the objectives of human trials ultimately influencing other themes.

Table 2 Additional quotes

Theme	Quote
1. Optimize the animal model	*"It always remains somewhat of a gamble. You tested it on animals, but animals are not exactly like humans."* [Parent, F7] *The lambs are extracted from the AAPT after four weeks, but are full-term by then. Infants would come out after four weeks and then what? Do they still go into the incubator?"* [HCP, F1]
2. Determine the objective of the first in-human trials	*"There should be room to fail. [...] It has to be clearly substantiated when [the trials start] with infants in critical condition to see if it works technically. It has to be accepted that things could go wrong."* [HCP, F2]
3. Carefully establish the research population	"*Then maybe say: only if you already have a child. If the cesarean section were to cause complications, it shouldn't be the reason that you can never have another child*." [Parent, F7] "*If you want to see whether this even works, you'll have to start with a group where the children are physiologically developing normally.*" [HCP, F2] *"Use the same criteria we currently apply to a pregnancy. At 23.5 or 24.0 weeks of gestation [...] don't go below that, otherwise you won't know what you're comparing."* [HCP, F2] *"Personalize per patient and parents if this would be a suitable option for the child and parents."* [HCP, F3]
4. Formulate stop criteria, success criteria and outcome measures	*"The end point should be really clear"* [HCP, F1] *"...you have immediate survival, but the long term—that is of course the real obstacle, that we simply don't know. And when do you then decide: this is less favorable?"* [Parent, F7] *"When is it considered successful? If the infant survives? If the infants survives the neonatal phase? Or is it about the long-term outcomes?"* [HCP, F2]
5. Determine the role for parents during the human trials with the AAPT	*"If you do not include parents, you might as well observe everything from a distance in an observatory"* [HCP, F2] *"Do they come for visits? Do they stay at home? [...] That's another consideration, you know. Because here with us, they are allowed to visit the NICU [day and night]"* [HCP, F1]
6. Develop protocols for the trial & address logistical considerations	"*Meeting their child will be very different than with the regular treatment after birth*" [HCP, F1] *"Maybe the infant deteriorates significantly while still in the placenta, whereas the infant could have spent his final moments lying on his mother's chest. You need to be ahead of that moment"* [HCP, F1] *"This is high-tech, you know, just like ECMO; we only have it in some centers"* [HCP, F5]

Discussion

This study represents the first empirical study into the perspectives of key stakeholders on what they consider important to consider before human trials of the AAPT should start. The results underscore the importance of clearly defining the objective of the human AAPT trials, as it significantly influences the design and execution of each phase.

Overall, participants often assumed that the trial should aim to demonstrate the AP's superiority over the current standard of care. This is known as a superiority trial aiming to demonstrate that the AAPT provides significantly better outcomes. These outcomes should not be limited to survival but should focus more on quality of life, which is also a crucial subject for further discussion. However, parents and HCPs also discussed that the aim of the trial should be to examine the technology's safety and effectiveness. A non-inferiority trial might be more appropriate in this context, as it aims to show that a new treatment is not significantly less effective than the standard approach (e.g., in terms of survival) while offering potential benefits, such as a lower risk of BPD or intraventricular hemorrhage.

The goals of a human AAPT trial will directly impact how the study is designed and conducted. For instance, if the aim is to compare AAPT with standard NICU care, researchers would need to select a different group of infants, use different outcome measures, and follow different study protocols than if the goal were solely to assess the technology's safety.[23] In a comparison study, the most suitable participants would be infants who have a reasonable chance of survival with standard NICU care. However, including these infants poses serious ethical concerns because the risks and benefits of AAPT in humans remain uncertain.

On the other hand, safety trials might focus on non-viable infants—babies who have no chance of survival with current medical care. While this approach could help assess the technology's safety without affecting infants who might otherwise survive, it also raises significant ethical dilemmas, such as whether it is appropriate to use AAPT in cases where survival is not possible.

The considerations outlined by our participants have notable similarities with existing legal frameworks and guidelines regulating trials, which are primarily ruled by national regulations and international standards such as Good Clinical Practice Guidelines.[24-26] These regulations describe that all preclinical research, including animal models, have to be validated to ensure safety and relevance before human trials begin.[24-26] This is reflected in the participants' concerns about the validity and translatability of the animal studies to humans, finding the evidence derived from these studies insufficient and the risk to human subjects unacceptable. So, before proceeding to human AAPT trials, consensus should be reached with key stakeholders when evidence on risks and benefits from the animal model is sufficient, which specific risks and benefits to prioritize, and when the trade-off between these risks and benefits is considered acceptable.

In addition, the legal frameworks emphasize fairness and justice as crucial factors in selecting a research population.[25] This aligns with HCPs' concerns and considerations regarding the research group selection. Typically, three distinct research populations can be recruited for human trials: 'healthy volunteers', 'seriously ill patients unable to benefit from standard of care', and 'patients with a stable disease'.[27,28] Selecting the research population depends on aspects such as the trial's scientific objective, the 'best data' criterion (i.e. most representative population) and the balance of risks and potential benefits.[28] Scientific justification for including certain groups is balanced against the moral obligation to minimize harm.[29]

In the context of AAPT, it can be argued that there is no 'single best population' for human AAPT trials, which is also evident in current literature.[11,12] For instance, the non-viable group has been considered more ethically justifiable, though concerns remain about the potential for prolonging the suffering of entities unlikely to survive.[8] On the other hand, De Bie et al. argue that a viable population may be more justifiable, particularly because the new technology is not a complete replacement for NICU care.[4] If the AAPT technology does not work as expected, and it would be possible for the viable neonate to be transferred to an incubator, this would help mitigate some of the risks but still does not resolve the ethical complexities of selecting the most appropriate cohort for these trials.

Additionally, the situation is uniquely complex as there are two patients to consider: the mother and the infant, requiring careful consideration of both parties' health and well-being.[13] Parents and HCPs discussed the criteria for including specific groups of infants in the human trials more extensively than the indications related to the mother or the placenta. The most proposed populations, 'non-viable infants' and 'viable with good prognosis', are most similar respectively to the seriously ill & the stable disease population. Even if an ideal group were to be established, the results of our study suggest that HCPs and parents may hold differing views on this matter, particularly regarding the potential inclusion of the 'viable with good prognosis' group which should be considered carefully in terms of the willingness of parents to participate in the human AAPT trial.

Establishing the research population for the AAPT trial presents specific challenges due to the involvement of two distinct participants—the child and the mother—each governed by their own ethical and legal frameworks. Additionally, the existing shared decision-making process with parents regarding treatment options for extremely premature infants must be preserved considering the legal requirements of the informed consent procedure.[30-32]This is further explored in another article of the TINY-3 study.[33] Consequently, it is imperative for stakeholders to carefully assess which group constitutes the most legally and ethically responsible research population considering the infant and mother.

Strengths and limitations

This is the first qualitative study on Dutch HCPs' and parents' perspectives regarding AAPT trials, offering unique insights. A various group of participants was interviewed, enhancing the diversity of perspectives. Furthermore, the multidisciplinary nature of the research team contributes to the study's strength.

This study also has some limitations. First, the findings may be contextualized within the Dutch sociocultural milieu, its associated societal values and restrictive approach regarding the resuscitation of the most immature infant, potentially constraining the broader perspective on this technology and its human trials.[34] Nonetheless, our research underscores the significance of stakeholder engagement and demonstrates the critical importance of reflective analysis of the results. Secondly, although we purposively sampled participants from obstetrics, the majority of HCP participants had backgrounds in neonatology. Another potential limitation is selection bias, as individuals with either strong negative or positive opinions about the AAPT may have been more likely to volunteer for the study. However, thematic saturation was reached and the results neither unequivocally endorse nor reject the AAPT suggesting balanced results. Third, while we reached thematic saturation, it is unsure if the identified themes encompass all possible conditions. Lastly, our interpretation may have been influenced by our own perspectives. However, we took steps to mitigate this by involving a multidisciplinary team and conducting multiple rounds of discussion to ensure a more balanced and reflective analysis.

Conclusion

This study emphasizes the importance of stakeholder involvement in responsibly designing human AAPT trials. Our findings underscore the importance of stakeholders reaching consensus on clearly defined objectives of human AAPT trials as these will influence critical decisions, regarding the research population, study design and outcome measures. Establishing this consensus among stakeholders is essential, shared recommendations will facilitate alignment of expectations and promotes engagement throughout all subsequent phases of the potential future AAPT trials.

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Chapter 8

Healthcare professionals' and parental perspectives on human artificial placenta technology-trials: counselling and informed consent

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Abstract

Background: The Artificial Amnion and Placenta Technology (AAPT) is developed to improve outcomes of extremely premature birth, with first in-human trials expected in the coming years. Empirical research with key stakeholders is essential for responsibly designing these trials. This study aims to discuss considerations for counselling and informed consent for the first in-human trials of the AAPT, discussing legal and ethical considerations.

Methods: A qualitative study using both individual and focus group interviews with HCPs and parents was performed. Interviews were thematically analysed.

Results: Fifteen parents and 46 HCPs were interviewed. The results are represented into key themes reflecting participants' perspectives on: (I) the moral and legal status of the subject treated in AAPT trials, (II) the first participant: the pregnant person, and (III) the terminology used to describe the technology. Furthermore, considerations around the informed consent process and counselling, including parental hope, are described. The findings suggest these factors are interconnected, as the moral and legal context surrounding AAPT trials influences the approach to counselling and informed consent.

Conclusion: Resolving key ethical and legal issues important for counselling and informed consent is essential for establishing parental right and the development of a responsible, ethically sound informed consent process.

Background

The development of the Artificial Amnion and Placenta Technology (AAPT) marks a potential advancement in perinatal care, as it has been shown in animal studies to delay the transition from fetal to extrauterine physiology.[1] As such, it has the potential to reduce complications associated with extreme premature birth and intensive care treatment.[2,3] For the first in-human trials that are potentially expected in upcoming years, it is crucial to establish an adequate counselling and informed consent process including the consideration of the legal and ethical implications that play a role.[4,5]

The informed consent process for trials in perinatal care involves thorough discussions between healthcare professionals (HCPs) and parents, covering the technical aspects of the AAPT, risks, benefits, alternatives and the possibility of not achieving the intended goal.[6,7] Human AAPT trials will likely be considered in cases of imminent extreme prematurity since it is developed for this indication. Currently, prenatal counseling provides parents information based on gestational age (GA) of their infant. For delivery at the limit of viability, parents are often faced with a decision between intensive care and comfort care depending on guidelines per country. Introducing AAPT into these already complex and emotionally challenging conversations, which are often taking place under intense time pressure, introduces a new layer of complexity.[5v]

So far, research on the AAPT predominantly has focused on its technological development[3], the challenges and results observed in animal studies[8-14], and theoretical ethical and legal considerations.[15-20] There is little literature, though, about the challenges and concerns regarding the design of AAPT trials.[5,18] Additionally, research incorporating the perspectives of key stakeholders in this field is lacking. The TINY-3 study aims to fill this gap by conducting a qualitative interview study to explore the perspectives of HCPs in perinatal care and parents who have experienced an imminent or actual extremely premature birth on the future human AAPT trials. This article focuses specifically on considerations for the informed consent and counselling in human AAPT trials, as well as ethical and legal questions that play a role in the challenges surrounding counselling and informed consent.

Methods

This research is part of the Dutch research project "Toward INdividualized care for the Youngest" (TINY-study). The TINY-3 aims to explore perspectives of different stakeholders on the AAPT as potential new treatment option for extremely prematurity. An extensive description of the methods can be found in *Supplemental material TINY-3, file 1* of this article and is also described elsewhere.[21] *Figure 1* displays the process and different phases of the TINY-3 study (*Supplemental files TINY-3, file 2)*.

In the first phase of TINY-3, a stakeholders meeting was conducted following a guidance ethics approach (*Intermezzo C*).[22] Following this stakeholder meeting, we carried out focus group discussions and individual interviews (phase 2) to further explore and expand on the main results of the stakeholders meeting.

Participants were recruited through the TINY-database with parents who have experienced an imminent or actual extreme premature birth in the past, the Dutch patient association Care4Neo, social media platforms and the researchers' professional networks. Inclusion criteria required participants to be either (I) perinatal HCPs or (II) parents who have experienced the birth of an extremely premature infant (GA <28 weeks).

An interview guide, based on the prior stakeholder meeting and the expertise of our multidisciplinary team, was developed. Interviews were moderated by 2-3 team members. Interviews were recorded and transcribed verbatim. The interviews were independently analysed and coded by AB and RK using a thematic analysis approach, following Braun and Clarke's guidelines.[23]

Results

Six focus group interviews with HCPs (n=46), two focus group interviews with experienced parents (n=10) and five individual interviews with an experienced parent (n=5) were performed. Among the HCPs were physicians, nurses, nurse practitioners, midwives, a psychologist and a pathologist, all from the field of neonatology and obstetrics. All parents had experience with an extremely premature birth or an imminent extreme preterm birth. Demographic information is presented in *Table 1A and 1B (Supplemental files TINY-3, file 4).*

First, we present ethical and legal considerations related to counselling and the informed consent process about the AAPT: (I) the moral status of the subject inside the AAPT with the potential legal consequences and terminology, (II) the first participant: the pregnant person, and (III) the terminology of the technology. Then, we describe considerations for the informed consent and counselling including the role of parental hope. According to our participants, these themes surrounding the AAPT and its clinical trials are inherently interconnected. This directly impacts how HCPs should approach counselling parents about AAPT trials. Furthermore, this also influences how parents approach their decision-making process when considering participation.

Moral and legal status of the subject treated during the AAPT trials

Parents and HCPs reflected on the subject's moral and legal status during the first AAPT trials. They emphasized the importance of establishing this status before the trials begin. All parents and some HCPs agreed that the subject should be considered a neonate, and therefore, legally recognized as being born. The following statements were presented to support this view: "*the definition of birth is the complete expulsion of the fetus from the moth-*

er's body", "*the baby has left the mother*", "*it is out of the mother's womb*", "*the umbilical cord has been cut*", "*it is outside the protected environment*", or "*the mother has delivered*". Parents associated 'being born' with the belief that the subject should be treated according to the rights and considerations typically afforded to any child. HCPs stated that establishing this status is crucial for clarifying the rights of the subject in the AAPT before human trials start. Furthermore, participants concluded that defining the subject as a neonate would eliminate any debate over terminology, allowing the subject to be simply referred to as a neonate. The status of 'neonate' and 'being born' was also linked by HCPs to neonatal care, thereby designating the neonatologist as the responsible HCP during the human trials. According to these participants, the AAPT should not be compared to an uterus but rather viewed as an advancement of the incubator.

In contrast, other HCPs argued that the subject in the AAPT should not be considered born, as "*it is more of a transfer*", "*the baby is not breathing*", and "*it retains the status of a fetus*". So, they suggested that it could be seen as a transfer to another fluid-based environment such as the amniotic sac and placenta, and thus falling within the field of gynecology and necessitating the involvement of gynecologists during the human trials. According to this view, the legal framework should be based on the rights of a fetus, with corresponding rights for the parents. In this context, it was suggested that developing a legal addendum specifically addressing this unique situation might provide greater safety and clarity.

One group of HCPs further debated the possibility of a 'transitional status', where the subject is neither fully born nor still a fetus. Participants stated that it would be necessary to develop a completely new legal framework, which may also lead to further discussion on the appropriate terminology to describe this transitional state.

Participants emphasized that, related to the status and corresponding rights of the (future) child, the rights of parents and HCPs should also be clearly established to protect them in decisions regarding the initiation or withdrawal of treatment during the human trials.

The first participant: the pregnant person

Especially HCPs worried about the first participant in the context of AAPT trials: the pregnant person. HCPs stressed that pregnant persons may be willing to accept significant disadvantages for themselves for the sake of their baby, far more than what we would ask of other patients, "*such as organ donors*". Furthermore, they were concerned whether you could ask a pregnant person to undergo a cesarean section to participate in the AAPT trial, without knowing the benefits for the subject. Some HCPs emphasized the damage that would be done to a woman and potential future children. As one HCP stated: "*I wonder if it's a promising development for the mother, especially considering the potential implications for following pregnancies if she undergoes a cesarean section at 24 weeks*". One HCP also noted that when parents opt for comfort care, a cesarean section is typically not performed. Some of the mothers were not willing to undergo a cesarean section or doubted if this

would be desirable in all situations. These concerns of participants made clear that the informed consent for mother and child are intertwined and some suggested two sequential informed consents.

Terminology to describe the technology

During discussions on the moral and legal status of the subject undergoing treatment in the AAPT, it became evident that this is also connected to the terminology being used. Participants reflected on whether labeling the AAPT as either a placenta or an uterus might shape the perceived nature of the technology, potentially influencing how we view the moral and legal status of the subject. In contrast, if the AAPT were considered an incubator, the subject might be viewed as a neonate. Moreover, a mother mentioned the terminology being important for the acceptance of the technology: "*When I first read about it, my immediate feeling was a bit like: I would replace the word 'artificial.' [...], I notice that people, myself included, tend to be kind of deterrent, because artificial is so distant from emotion and humanity*".

Informed consent and counselling

Participants discussed what they considered essential in the informed consent and counselling about the AAPT trials. Parents emphasized that the informed consent about the AAPT-trial should be "*good, objective and personalized*".

First, conditions for the process of counselling and informed consent were discussed. HCPs considered it important to estimate if parents could comprehend what participating in a trial with the AAPT would mean, which includes parents understanding the language and being able to understand all the information. Furthermore, both parents and HCPs agreed that time to counsel parents is essential, preferably time to counsel parents more than once, for parents to consider the decision about participating in first in-human trials carefully, and for involving other disciplines. As one parents stated: "*[Counselling should not take place] at the most urgent moment, but [should take place] when you have a more calm feeling, so that you also have time to take a look at the information about the AAPT*". It was suggested that parents would be counseled during a high-risk pregnancy about the human AAPT trials in the event of extreme premature birth, or that the research population be adapted to include individuals who would have sufficient time for counseling.

Furthermore, it was discussed how the option of human AAPT trials would fit in the current counselling and decision between early intensive care treatment and palliative comfort care. Some participants thought it should be given as an additional option alongside intensive care and palliative comfort care, while the others preferred to present the option of the AAPT trial only after parents opted for intensive care treatment. In *Table 2*, the different reasons per option are summarized supported by quotes. *Figure 2* gives an overview of these different pathways. Notably, there was no mention of discussing AAPT after parents had made the decision to opt for palliative comfort care. Participants agreed there should

be one universal approach for counselling parents and the moment to present the option of the AAPT trials.

Table 2 The timing of offering the option to participate in the human trials of the artificial amnion and placenta technology

Moment of giving the option to participate in the human trials of the AAPT	Reasons of the participants
AAPT trial as option in addition to intensive care treatment and palliative comfort care	**Been given all the options:** "*I would have wanted to know [all the options]. (...) Even if you choose not to, I still would have wanted to know. That you have those three options" [*parent]
	Try the artificial placenta instead of comfort care: "*If someone chooses palliative care, but still wants to try the artificial placenta, you never know how it may change the parental perspective. If they decide for AAPT and see after a few weeks: it's going well in the AAPT, maybe they will opt for active treatment afterwards***"**[HCP]
	Different treatment: "*[The trial with the AAPT] is really different from the current treatment we are providing [in case of starting intensive care treatment] now*" (HCP)
	Intensive care treatment in case the AAPT fails: "*It is an option alongside intensive care treatment and comfort care, because if AAPT doesn't work, then you can still [stop with the trials and] switch to intensive care treatment, [so it is not a decision between treatment with an incubator, or with the AAPT].*" [parent]
AAPT trial as option after decision intensive care treatment	**Unknown outcomes:** "*..because you don't know yet what it's going to be, what the outcomes will be in the AAPT*" [parent]
	Clear decision: "*That parents at least have the choice not to go down that path, and that it's clear whether it's left or right. With one, you treat, with the other, you don't*" [HCP]
	Form of active care: "*but for me, it falls into that active care category*" [HCP]
	Confusing to give another option: "*So comfort care or active care. And then from there explain the difference between those two. Otherwise, you really can't see the forest for the trees, right?"* [HCP]

Abbreviations: AAPT = artificial amnion and placenta technology; HCP(s) = healthcare professional(s)

Second, conditions for the content of the counselling were formulated. Parents and HCPs agreed it was essential to be honest about the experimental character and the lack of long-term data about the effects of this treatment. Moreover, the role of parents during the AAPT-trial, the need for a cesarean section with the additional uncertainty about the timing of delivery and the associated risk of a medically induced early delivery, and what to expect during treatment (e.g., possibility to touch your infant) should be discussed to prepare parents according to both parents and HCPs. Parents were opposed to discussing the risks based on the animal testing model for those who want to know statistics. Other participants were uncertain about whether you should mention this, especially about when you should bring it up during counselling: "*That's probably a very strange moment when you*

suddenly start talking about animals. [...] For people who like to hear the numbers, that might be something... But it's really difficult, because when do you bring that up?"

Lastly, the discussion focused on potential considerations for parents regarding participation in human trials, as presented in *Table 3*. Parents felt it would be an impossible choice, because neither short-term nor long-term data could be considered, given the fact that the AAPT had not yet been tested on humans. Parents worried about the emotionally overwhelming state when they faced an imminent extremely premature birth. They had based their decision when facing their imminent extremely premature birth on the instinct to save their child. One parent felt that parents could not be asked to make this decision.

Parental hope

Some parents favored the information about the potential benefits of the AAPT for their child. In the absence of specific statistics and probabilities, they speculated that the potential outcomes of the AAPT could be more favorable than those of current treatments. HCPs could envision parents viewing this decision as a matter of life and death, believing that the AAPT might offer the best chance for their child's survival or believing that it would be the 'better' option.

Figure 2 gives an overview of these different pathways. Notably, there was no mention of discussing AAPT after parents had made the decision to opt for palliative comfort care. Participants agreed there should be one universal approach for counselling parents and the moment to present the option of the AAPT trials.

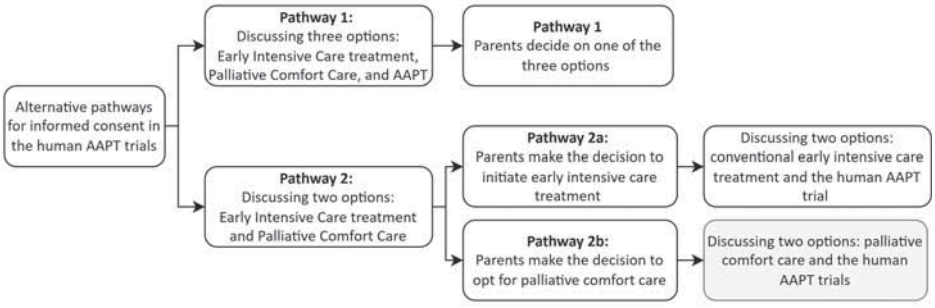

Figure 2 An overview of the different consent pathways, including, in grey, the pathway that was not discussed by the participants but could theoretically be an option in the context of 'nothing to lose'. The fact that the pathway via palliative comfort care was not mentioned may be attributed to the way the interviews were conducted, as in some interviews participants spontaneously brought up when this should be offered, while in others the interviewers had to ask about it explicitly, which may have caused a probing effect.

Table 3 Pro and contra arguments of parents whether they would be willing to participate in human artificial amnion and placenta technology trials

Pro	Contra
AAPT may give a better outcome: "*It comes down to the fact that we had already decided that [child's name] was going to pass away. (...) You could take the chance. The outcome was already negative, so it can only get better*"	**Experience with good outcome after current treatment:** "*With my background, I think I wouldn't choose this in the experimental phase, because I know it can also go well at 24 weeks.*"
Risk of the cesarean section is acceptable because this decision is for this child, not for future children: *"[This is about your child right now.] Whether there comes a brother or sister at a later moment, you would never know that. That's not a given fact. But if you can save these children with it: bring it on"*	**Cesarean section:** "*If a C-section needs to be done, it apparently isn't good for the next pregnancies. If it's the first time, with a premature birth, then I wouldn't do it"*
Trust in medical science: "*Trust that this has been carefully thought through, so let's give it a try because the situation is already unpromising"*	**No long-term data/to risky:** "*You decide to take a great risk with a treatment [in a trial setting] of which nothing is known yet*"
To create statistics for others in the future: "*For me, I would like to contribute to actually creating statistics for the future and maybe you also benefit from it with your own child*"	**Own good experience:** "*I was in an incubator myself and turned out well. [So I would go for] the safe option*!"
To prevent suffering associated with the conventional NICU-treatment: "*So much is already asked of a baby at 24 weeks; laying in the incubator, with lots of injections, and the struggle to breath, with the potential risk to have to go back on the ventilator. (...) And if they could just rest in something like a womb-like environment for another four weeks, where they don't have to breathe and aren't poked from all sides, just can grow, wouldn't that be much better?"*	**Test baby:** "*Not wanting to be the 'first test baby'*
No disadvantages: *"No known disadvantages."*	

Abbreviations: AAPT = artificial amnion and placenta technology.

DISCUSSION

This article focused on the stakeholders' formulating considerations pertaining to the informed consent and counselling surrounding AAPT trials in humans. In this discussion section, the impact of the AAPT on existing concepts and boundaries in the context of extreme premature birth are presented and challenges in counselling and informed consent are further discussed.

Changing boundaries and concepts

With the introduction of the AAPT, the (ethical) landscape of managing extreme prematurity may fundamentally change. Existing concepts (e.g., being born or not) and used terminology (e.g., neonate or fetus) may no longer adequately capture the complexities introduced

by the AAPT, as these terms often imply moral boundaries that the AAPT challenges.[15-17] Our results reveal a tension between how parents and HCPs perceive these concepts. All parents tended to view the child as "born," which is understandable given the difficulty in perceiving infants who have left the womb as anything other than being born. In contrast, some HCPs saw the status of the subject in the AAPT as 'not being born/a fetus', which could mean parents have to reframe their entire process and experience of birth into a different category. This view of the subject having the moral status of a fetus would not change anything in the legal position of the subject after transferring from the womb to an AAPT.[15,17,19] A fetus is not legally recognized as born and therefore has no independent rights.[19,24,25] However, it could impact the distribution of parental rights. In most countries the rights of a father change when the child is legally born.[19,26] Furthermore, the notion that the pregnant person's bodily autonomy remains the central determining factor for the subject that is no longer inside the pregnant person but also not legally born yet, becomes harder to justify, raising questions about the balance of rights in this unique context and the potentially need of an addendum to the law. Lastly, referring to the subject as "born" may be more straightforward, as parents are likely to view the subject as their child, and an established legal framework would already be in place.[19,27,28]

For the design of the AAPT trials, and consequent counseling and informed consent, it is crucial to have a clear understanding of the ethical and legal position of the patient(s) in the trial, the technology and the responsibilities and rights of all involved parties.[5] Without establishing this beforehand, it would be difficult to effectively communicate with parents about AAPT trials and what participating in a human trial means legally.

Challenges in the informed consent and counselling

After discussing moral and legal challenges surrounding the informed consent, it is essential to look at the process and content of the counselling and informed consent. Generally, consent for participation in clinical research is considered valid when the following criteria are met: competence, information, understanding and voluntariness.[29] The conditions formulated by our participants – 'ensure parents can fully comprehend the information provided' and 'allow sufficient time to counsel parents' – emphasize these widely accepted requirements for informed consent in medical research. For disclosure of sufficient information, participants believed a certain minimum amount of information should be provided to parents during counseling about the trials, such as the experimental character, lack of short- and longterm data, the role of parents during the trails and the necessity of an cesarean section. Meeting these criteria could be challenging and difficult to assess.

Our participants' considerations of the informed consent for the human AAPT trial are underscored by those of other high-tech medical perinatal trials, such as the Management of Myelomeningocele Study (MOMs) trial and Extra Corporeal Life Support (ECLS) trials.[6,30-32] These trials also show the importance of having time to counsel parents, to start counseling in time (e.g., during high risk pregnancy) and to select the research population based on

the established fundamental conditions for counselling and informed consent.[30,32] With the MOMs trial, parents benefitted from discussing their moral concerns during ethical consultations as part of counselling and informed consent, highlighting the advantage of a multidisciplinary approach.[33] The ECLS trials provide valuable lessons on complexity of information, especially in such emotional overwhelming situations, which could lead to the misunderstanding of parents about the nature and purpose of the trial.[34] Both trials also discussed concerns about voluntariness and maternal well-being indicating parents viewed consent requests as an implied preference for the new treatment, leading them to feel they had no choice but to consent due to the lack of alternative options.[35,36] The way consent is requested can lead parents to feel that a treatment—like ECLS, which could be lifesaving—is the only acceptable option, leaving them no choice, even though consent should be fully voluntary.[36] Furthermore, the MOMs trial demonstrated that pregnant individuals were often willing to take on significant personal risks during pregnancy to benefit their unborn child.[31] Finally, literature on complex decision-making in pediatrics indicates that parents find sharing responsibility in decisions particularly challenging in highly technical and urgent situations.[37,38]

These high-tech medical perinatal trials provide some guidance for the informed consent in the AAPT context, such as the recommendation of a multidisciplinary approach and addressing challenges in voluntariness and the pregnant person as participant in a trial. However, other significant challenges remain such as the complexity of the information and the timing of consent, and ongoing discussions are essential to find solutions, make recommendations and develop a comprehensive informed consent process. Evaluating and updating the counselling and the informed consent should also be an essential part of the human trials.

As parents and HCPs navigate these high-stakes decisions, it may be necessary to adapt existing counselling informed consent processes.[39-41] The emotional stress, technical complexity, and urgency of the intervention may hinder complete disclosure and increase the risk of therapeutic misconception.[42,43] Parents may favor the potential advantages over disadvantages, misunderstanding that clinical research aims to generate generalizable knowledge, rather than individual benefit.[44,45]

Potential therapeutic misconception

The results show the inherent difficulty of separating a research setting from a care setting in the context of the AAPT. Both the answers from parents and HCPs reflect this challenge, as their responses often seem to be shaped by the expectation—or at least the hope—that participation in the human AAPT trials would yield personal benefits for the child involved rather than to advance scientific knowledge. This concern is also described in literature as therapeutic misconception. Therapeutic misconception may constitute (I) an unrealistic expectation of personal benefit, based on misunderstanding of the nature of the clinical trial or (II) the failure to realize that research is the primary purpose of the clinical trial.[46]

Thus, it is essential to clearly differentiate between the goals of clinical research and standard therapeutic treatment.[47] Furthermore, it should be explicitly communicated that the trial's primary aim is to gather knowledge, which may not directly benefit the patient, while standard treatment focuses solely on the patient's care.[48] Furthermore, providing enough time for discussion and reflection can also help mitigate the pressures that might lead to therapeutic misconception.[49] By implementing these strategies, the likelihood of therapeutic misconception can be reduced and the informed consent process for AAPT trials would be aligned with the best practices learned from similar research.

Strengths and Limitations

This study has several strengths. It is the first qualitative paper providing a unique insight into the perspectives of HCPs and experienced parents regarding the AAPT trials. The TINY-3 study benefits from a diverse selection of participants giving a broad range of perspectives on the development of the AAPT. Additionally, the multidisciplinary research team adds to the strength of the study by interpreting the results from different perspectives.

However, there are also limitations to consider. Firstly, certain findings may be influenced by the specific Dutch context and societal values, potentially limiting the perspectives on this technology to the Dutch perspective. Secondly, the recruitment process predominantly attracted HCPs working at the NICU. Despite the apparent achievement of thematic saturation, it remains unclear whether the obstetrical and neonatal perspectives were equally represented. While the overall number of parents that were interviewed seems limited, we were able to interview parents with varying backgrounds and experiences, resulting in a range of perspectives from experienced parents that contributed to data saturation. Additionally, individuals with strong negative opinions about this development may have been more inclined to volunteer for the study, potentially biasing the results.

Conclusion

This article offers insights into stakeholders' perspectives on counselling and the informed consent related to future human AAPT trials, discussing ethical and legal considerations and complexities. The discussion about the moral status of the subject in the AAPT underscores the need for consensus on important concepts before proceeding to further designing the human AAPT trials. Resolving such matters is crucial for defining legal challenges like the rights of all involved parties in potential future trials, and therefore the process of counselling and informed consent. The complexities of these issues make it clear that the discussion around informed consent must be handled carefully with all stakeholders involved. Ongoing dialogue is essential to develop a responsible and ethically robust framework for counselling and informed consent for the human AAPT trials.

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Chapter 9

The ethical concerns of Dutch perinatal healthcare professionals and experienced parents regarding artificial amnion and placenta technology

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Abstract

There is ongoing research into so-called artificial amnion and placenta technology (AAPT); the hope is to support extremely premature infants by mimicking the in utero environment, potentially reducing mortality and morbidity compared to conventional care. While implementation into clinical care is still some way ahead, this study seeks to understand the key ethical concerns of parents and healthcare professionals (HCPs), crucial for guiding the responsible development and application of this technology. To address these concerns, eight focus-group interviews and five individual interviews were conducted with 46 healthcare professionals working in perinatal care and 15 parents who experienced an actual or imminent extremely premature birth. The interviews were recorded and transcribed verbatim. The transcripts were thematically analysed and revealed key concerns, represented by the following five themes: (1) a slippery slope, focusing on the impact of AAPT on viability, (2) human nature and unnaturalness, (3) risks and benefits for infant, mother and beyond, (4) replaceability of the mother, and (5) resource allocation, inequality, and inequity. Dutch parents and HCPs expressed a range of viewpoints regarding the implementation of AAPT, ranging from opposition to cautious optimism. Addressing these concerns and integrating stakeholder perspectives is essential for guiding responsible policy-making for this emerging technology, and could also impact its acceptance.

Introduction

In recent decades, several research groups around the world have been engaged in research on the development of a system that mimics the function of the amniotic sac, amniotic fluid and placenta: the artificial amnion and placenta technology (AAPT), also sometimes referred to as ectogestation, or partial ectogenesis.[1-3] AAPT would potentially be able to provide support for infants born extremely prematurely, in a way that is more similar to the in utero environment (retaining fetal circulation), and with less mortality and morbidity than conventional intensive care support.[1,3,4] Animal studies show promising results, and there is the potential for first in-human trials in the near future.[5-7] Such trials are essential to determine whether the AAPT would be safe and effective in extremely premature newborns.

Although the AAPT is still far from implementation into clinical care, we believe it is important to start thinking about the implications of its clinical use.[8] There is a growing body of literature identifying a variety of ethical issues and implications of the AAPT.[9-13] Pressing issues for clinical translation include informed consent for novel and experimental technologies and equity of access to the technology.[14] However, there is no literature on which ethical issues are of most concern to stakeholders. This study aims to contribute to filling this gap by obtaining insight into the primary ethical concerns of parents who have experienced a threatened or actual extremely premature birth and of healthcare professionals (HCPs) involved in perinatal care for extremely premature infants. Exploring these ethical concerns will help with critically reflecting on the development of this technology.

Methods

TINY-study and study design

This article is part of the Dutch research initiative "Toward INdividualized care for the Youngest" (TINY-study).[15-18] The TINY-3 study focusses on the ethical concerns and considerations surrounding the potential use of the AAPT as a new treatment for extremely premature infants.

Figure 1 illustrates the methodological framework of the TINY-3 study, which consisted of different phases (*Supplemental files TINY-3, file 2)*. The initial phase involved a stakeholder meeting using the Guidance ethics approach (*Intermezzo C*).[19] After this, phase 2 consisted of focus group discussions and individual interviews to deepen the analysis of the ethical issues highlighted during the stakeholder meeting. The study's findings are presented across four interconnected articles. The other articles explore the crucial considerations that must be addressed before moving forward with AAPT trials and focus on the counselling and informed consent process.[20,21] This article extends that work, focusing specifically on the most urgent ethical concerns and considerations of the AAPT after implementation into clinical care, as identified by participants.

Selection of participants

Participants for this study were recruited through various channels as described in *Supplemental material TINY-3 file 1*. Eligible participants were HCPs involved in perinatal care or parents who experienced an actual or imminent extremely premature birth (before 28 weeks gestation).

Data collection and analysis

A comprehensive interview guide was developed (*Supplemental material TINY-3 file 3*), informed by both the stakeholder meeting and the expertise of the multidisciplinary research team. Two to three members of the research team moderated the interviews, which were recorded and transcribed verbatim. Analysis of the transcripts followed thematic content analysis as described by Braun and Clarke, using both deductive and inductive coding.[22] The coding was independently performed by researchers AB and RK. The results are supported by quotes that were translated from Dutch to English by the authors.

Results

We conducted six focus group interviews with HCPs (n=46), and two focus group interviews (n=13) and five individual interviews with experienced parents. The HCPs represented various specialties, and parents had different experiences with extremely premature birth. Demographic information is presented in *Table 1A and 1B (Supplemental files TINY-3, file 4).*

Themes that emerged from the data focus on ethical concerns and considerations relating to the potential future use in standard care with AAPT, namely: 1) slippery slope, 2) human nature and unnaturalness, 3) risks and benefits, 4) replaceability of a mother, and 5) resource allocation, equality and equity. Parents expressed mixed views on the development of AAPT, generally leaning towards optimism. HCPs exhibited more scepticism, ranging from outright opposition to the development of AAPT among some professionals, through to others who recognized the potential of the technology, albeit with significant concerns.

Slippery slope

A great concern of both parents and HCPs was a 'slippery slope', suggesting that the development of the AAPT will lead to a chain of consequences. During the interviews, participants asked the following questions: "*How far are we willing to go?", "What is the limit?", "How early do we want to resuscitate children?"*, or *"What is still acceptable?"*. The HCPs and parents argued that with the development of AAPT, the limit of viability would likely go down. The HCPs were anxious that it would ultimately lead to full ectogenesis.

Human nature and unnaturalness

The interviews revealed a strong sentiment among HCPs and parents regarding the overstepping of natural boundaries (in Dutch *"Maakbaarheid van de wereld").* HCPs emphasized how artificial and mechanical the world has become. In this context, one HCP reflected on

extremely premature birth: "*The question is: is this normal? In nature, a baby animal will not survive extremely premature birth. We are the only species that live because we think we have the right to do so*." The perception of the world as increasingly unnatural was a source of concern, as some felt that there is no point of return with the development of AAPT, which is also an example of the previous theme 'slippery slope'. As a HCP stated: "*If you say yes to this, it only gets more artificial*", while other HCPs recognised the overlap with current practice asking: "*What makes this so different from treating 24-weekers*?".

HCPs and parents discussed the tension between keeping infants alive and recognizing the limits of interventions and technology. As one HCP noted: "*As people, and especially as HCPs, we tend to fix things*." Parents echoed these concerns, with one parent reflecting, "*Sometimes we go a bit too far*" and another admitting "*I find it complicated to knowingly keep children alive [just] for the sake of keeping them alive*". The participants had concerns about over-intervention, with both groups asking how far society should go in shaping human life through technological means. One parent stated: "*With the experience I have now, I think we should let nature take its course*." HCPs acknowledged that death is a natural part of life, as one parent pointed out: "*It is also okay to die at some point*".

In contrast, several parents and HCPs noted that while this technology may initially feel very unnatural and overstepping natural boundaries, it is ultimately attempting to replicate something inherently natural. As one HCP asked the group: "*Is this really artificial, or do we just call it artificial because it's different from the current way we do things?"* HCPs, in particular, compared it with the fact that current care practices are themselves also unnatural.

Risks and benefits

The potential for an increased number of iatrogenic premature births in the context of AAPT was a concern especially among HCPs, as it appears that a caesarean section might be required to transfer the baby to the AAPT-device. They worried that the necessity to perform a caesarean section could lead to more frequent, possibly unnecessary, premature deliveries. One HCP remarked: "*You're subjecting the mother to a caesarean and potentially taking the baby out too early*". The HCPs were apprehensive that the presence of AAPT might prompt earlier interventions in cases where waiting longer might be considered safe under current care practices. As a result, HCPs mentioned that infants who otherwise would have remained in utero longer might instead be delivered by caesarean in the context of AAPT, which "*could cause more harm than it solves*". One HCP asked, "*Is a caesarean really necessary? I still don't see the benefit over a vaginal birth*."

Parents and HCPs discussed the weighing of the uncertainty of outcomes against possible risks and negative consequences, such as impacts on parent-child bonding. Some parents indicated that if such technologies could prevent specific complications, they would find the possible risk and negative consequences of AAPT worthwhile. However, others questioned whether the risks associated with interventions needed in the context of AAPT,

like performing a caesarean section at an extremely early gestational age, were justified given the uncertain outcomes.

Replaceability of a mother

Both parents and HCPs discussed the idea of the mother's replaceability by AAPT. Some HCPs expressed concerns about how this would impact the often existing guilt of the mother, with one HCP stating, "*[Mothers] may think the machine is better than their own body*", suggesting that the mothers may perceive the technological interventions as more reliable or efficient.

Parents discussed that technology may negatively alter the maternal experience of the pregnancy, including the bonding with the child. They also emphasized that technological replacement may "*take away how special a pregnancy is*" and detach mothers from their natural connection with their babies during pregnancy.

HCPs expressed scepticism about the possibility of replacing the natural process, describing it as "*arrogance to think you can mimic a normal pregnancy*". They highlighted the complexity of the interaction between mother, child, and placenta, stating: "*That is so subtle, dynamic... I cannot imagine that you can mimic this so specifically without impacting future illnesses*."

Resource allocation, inequality, inequity

HCPs argued that AAPT may not be a desirable development because of the costs that will be involved. They wondered whether the costs of this high-tech treatment outweigh the benefits. The money could also be invested differently, as one HCP suggested: "*Perhaps a fraction [of what is spent on this technology] could also be allocated to improving the care of current 24-week preterm infants. I believe that step should come first".* It was noted that poverty is widespread, and healthcare is already very expensive. With this development, costs are expected to rise further, potentially leaving even more people unable to afford healthcare. This may lead to AAPT being a treatment for the rich people in certain parts of the world.

Furthermore, parents added that this money may be better spent on alleviating or preventing the burden for people who are already struggling in life. HCPs mentioned the fact that there is no budget to extend the follow-up care for individuals that are born extremely prematurely and found it incomprehensible that all this money would be spent on this development instead of on the follow-up first.

With selecting a particular group as research population (i.e., those currently at the borderline of viability), parents worried about the exclusion of other groups of extremely premature infants: "*So, there are also children born at 24, 25, or 26 weeks who simply cannot participate because [certain circumstances would make them] not eligible, right?".* The HCPs were particularly concerned about the exclusion of infants based on the allocation of re-

sources. For example, if the care with AAPT would be centralized in one centre, a baby would be excluded when born in another centre. This would be unfair according to them.

Proportionality emerged as a significant ethical concern of the participants, which was also linked to issues of inequity. Both parents and HCPs questioned whether the drive to improve care and further develop technologies is justified considering potential financial, logistical, and personal implications for society, healthcare systems, the infants and their families. Concerns were raised about the substantial financial and human resources invested in these technologies, which could arguably better be allocated to addressing other pressing societal needs, such as poverty reduction and shortages. As one HCP noted, "*You have to train people [...] There's already a huge shortage [of personal in healthcare] —where will we find these people*?"

Furthermore, several HCPs highlighted concerns about global health equity, feeling it is disproportional to focus on high-cost technological advancements in some regions while basic healthcare infrastructure remains underdeveloped in other parts of the world.

Discussion

Although there has been considerable discussion of the ethics of AAPT, this is the first study to explore in detail the perspectives of parents who have faced (imminent) extremely premature birth and of HCPs working in perinatal care who might be expected to use this technology. Overall, participants' views on the desirability of the development of an AAPT varied from being against this new technology to acknowledging the potential of this technology, although with significant concerns. Concerns that emerged from interviews included the potential impact on (the limit of) 'viability', the risk of overstepping natural limits, the balance of risks and benefits, and issues related to resource allocation, equity, and access to care.

Viability

One of the key concerns among HCPs was the potential impact of AAPT on the threshold of viability for extremely premature infants (i.e. the earliest gestational age at which premature infants can potentially be saved). This concern may be linked to the relatively conservative nature of current Dutch views on medical care at extremely preterm gestational age.[23] Previous studies have observed that Dutch professionals tend towards maintaining the current threshold of 24 weeks due to the perceived lack of good outcomes.[17,18,24] Concerns about this technology may overlap with a more general suspicion of the use of advanced medical techniques to save increasingly premature infants and the implications of saving those infants. If the threshold of viability were shifted, this may have implications both for neonatal care (i.e., whether it would be permissible to withhold survival focused care at parental request), and for obstetric care (i.e., whether abortion would be permissible at a certain gestational age).[25]

Our findings are in line with a previous quantitative survey of Australian HCPs. This study revealed that professionals anticipated that AAPT would shift the limit of viability. However, they expressed ambivalence about this potential change and whether the adoption of AAPT should become standard practice.[26]

However, is the concern about viability realistic? One of the leading research groups in AAPT has emphasized that their aim is not to alter the limit of viability.[2] They imply that it would be used to improve outcomes for infants who currently receive conventional support. Nevertheless, it seems plausible that, if successfully translated to humans, AAPT could enable the survival of extremely premature infants who could not previously have been saved. This may apply even if it would not intentionally be used to alter the limit of viability. For example, if AAPT demonstrates efficacy for infants born at 22 weeks in a country where infants at this gestational age are regularly treated, that may have implications for countries like the Netherlands, with a more conservative viability limit of 24 weeks. Consequently, the introduction of AAPT could challenge established ethical, medical, and societal standards.

It is essential to establish clear policies and ensure that any adjustments to viability thresholds are carefully considered before AAPT is implemented in clinical care. It may be important to clarify the relationship between neonatal treatment and thresholds for access to abortion.[27] However, it is not clear that concerns about the limit of viability are strong reasons to avoid pursuing AAPT. For one thing, there are strong practical, biological and medical constraints that entail that at least in the short-medium term, the technology is highly unlikely to dramatically alter the limit of viability (i.e. save infants much earlier than the current physiological limits).[26] Secondly, the mere fact that the technology would make it possible to save more premature infants would not in itself provide a reason not to pursue it. Advances in neonatal intensive care in the last five decades have shifted the borderline of viability from 28 to 22/23 weeks. But that fact in itself does not give reason to regret such advances.[26]

Natural limits

Secondly, concerns about AAPT overstepping natural limits echo broader Dutch societal fears of disruptive medical technologies, often framed as "playing God". Related to this is also a diminishing resilience and societal acceptance of the things that remain 'out of our control'. Similar concerns from Dutch stakeholders have been documented in discussions about CRISPR, where the ability to edit genes is viewed by some as crossing ethical boundaries due to its profound implications on human life and the natural order.[28] Reproductive genetic technologies, such as in vitro fertilization and embryo selection, have likewise faced initial resistance rooted in fears of tampering with human natural reproductive processes, although societal acceptance has grown as these methods proved their utility and safety.[29-31] A historical parallel can also be drawn with organ transplantation, which was initially perceived as unnatural and morally contentious before becoming a routine and life-saving intervention.[32] Moral concerns in this debate were solved by improving treat-

ment and outcomes through technological innovation.[32] These examples suggest that while initial resistance to the AAPT may reflect values about the sanctity of natural processes, acceptance may increase as the technology demonstrates tangible benefits and aligns with ethical safeguards. Addressing these concerns and integrating stakeholder perspectives is essential for guiding responsible policy-making for this emerging technology, and could also impact its acceptance.

Risks and benefits

Thirdly, participants were concerned about the uncertainty associated with the health benefit balanced against risks of this technological development. The potential benefits for the infant could be substantial, though they remain uncertain at this stage, while potential harms include iatrogenic extremely premature birth, the burden on the mother and potential negative consequences for the infant, the parents, the family and society. This theme reflects broader concerns in the literature about the balance between potential benefits of perinatal technologies and the risks for both the infant and the mother.[33]

One challenge, particularly in the early stages of developing this sort of technology, is the profound uncertainty surrounding its risks and benefits. This ambiguity complicates ethical decision making regarding the appropriate timing for offering the therapy. Once there is some accumulated experience, a different issue is that risks and benefits may be distributed unevenly. As with fetal therapies or fetal surgery, AAPT does not offer direct medical benefits for the pregnant person and may introduce significant medical risks. How should risks to the mother be weighed against benefits to the foetus/infant? If there would be an evident negative risk-benefit balance for mother and infant together, it may not be ethical to offer treatment. However, if the risks are more finely balanced - where the benefits to the foetus/infant may outweigh the risk for the mother and infant, then the decision ultimately comes down to the informed consent of the mother through shared decision making, as this would make it a preference-sensitive choice. This process must involve thorough discussions about values of all parties involved, the risks she is willing to accept for herself and for her infant, and the potential benefits for the infant.

Resources

Lastly, reasonable use of resources was a key concern for both parents and HCPs, particularly regarding the investment of funds and personnel in the development of AAPT. Stakeholder concerns reflect broader challenges in healthcare resource allocation, where the balance between innovation and equity must be carefully navigated. A method to evaluate and allocate societal investment could involve cost-effectiveness analyses, which often require statements on the monetary value of human life. For AAPT, such an analysis would need to compare the cost-effectiveness of standard neonatal intensive care unit (NICU) treatments and AAPT. Whether this technique is cost-effective will depend on how much it costs, and also on its incremental benefit. One critical consideration for AAPT is the value placed on saving the life of extremely premature infants around or even prior to

the current limit of viability.[34,35] On usual analysis, conventional forms of NICU, even for the most premature infants, are highly cost-effective because they typically yield many years of life, and the majority of survivors are not severely impaired, resulting in a high amount of quality-adjusted life years.[36] However, some of the HCPs and parents questioned whether resources should be spent on saving the lives of these premature infants. This might indicate that decisions about who to treat are connected to broader questions and dilemmas about resource allocation, moral status and social value placed on very immature lives. Such dilemmas inevitably involve determining who should be included or excluded, which in turn raises the critical question of how such decisions can be justified. One study found that the life of a premature infant was valued less than that of older children, such as a two-month-old or a seven-year-old, reflecting both the uncertainty of outcomes of an extremely premature infant and societal attitudes toward this group.[37] It is conceivable that some societies might choose not to invest in AAPT or related technologies because they place greater value on healthcare for older individuals. However, this would be controversial, and conflict with approaches that emphasise the intrinsic worth of all lives and the unique vulnerabilities of extremely preterm infants.

A different concern, expressed in particular by the HCPs in this study was that the development and implementation of AAPT would exacerbate global health inequalities, as its advanced capabilities would likely be concentrated in high-income countries, where resources for NICUs are already well-established. In low- and middle-income countries (LMICs), where NICUs are scarce or poorly equipped, access to such cutting-edge technologies would remain out of reach for the majority.[38] This disparity mirrors existing inequities in neonatal care, where infants in LMICs already face significantly higher mortality rates due to the lack of advanced interventions.[39] However, these concerns are not necessarily sufficient ground to halt the development of AAPT. Such concerns could be addressed by prioritizing strategies that promote equitable distribution and support for NICU-infrastructure development in LMICs. To a certain extent it then becomes an empirical question whether that can be combined with further developing the AAPT (depending on, for instance, where the funds needed to prioritize strategies to promote equitable distribution need to come from).

Strengths and limitations

This study is among the first to qualitatively explore HCP' and parents' ethical concerns on care with AAPT. A diverse group of participants was interviewed, enriching the variety of perspectives. Additionally, the multidisciplinary approach of the research team strengthens the study's credibility.

However, the study also has some limitations. First, results are dependent on personal moral perspectives of the participants and the results must be interpreted against the sociocultural background of the Netherlands and the physicians' professional field. However, in the context of other technologies and in other countries, certain ethical concerns

which arose during these interviews, such as overstepping natural boundaries, allocation of resources, equality and equity, are also very relevant concerns. Whether these stakeholder concerns can be generalized to other countries remains to be determined. Second, while participants from obstetrics were purposefully included, most HCP participants had backgrounds in neonatology, potentially narrowing the range of professional insights. Another possible limitation is selection bias, as individuals with strong positive or negative opinions about AAPT may have been more inclined to participate. However, thematic saturation was achieved, and the results neither unequivocally support nor oppose AAPT.

Conclusion

Exploring the perspectives of relevant Dutch stakeholders allowed us to identify key ethical concerns and considerations surrounding the potential implementation of the AAPT. Recognizing these concerns is essential to understanding the underlying values and normative dimensions that will shape its acceptance and impact. While these concerns are critical in order to minimize potential negative ethical and societal implications, they may not provide reasons to slow down the development of AAPT. Equally important is the uncertainty regarding how individuals in the perinatal care field—both those who deliver high-tech care and those who have received it—perceive this technology. Perspectives of these stakeholders ranged from ethical opposition to cautious optimism about its potential. By acknowledging and integrating these diverse viewpoints into the development process, we can foster a balanced and inclusive approach that respects stakeholder values in advancing or halting further technological developments. These findings can provide a foundation for formulating policies and guiding further discussions to ensure that the potential further development and implementation of AAPT happens responsibly and equitably.

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Supplemental files TINY-3 study (chapter 7-9)

- File 1: Detailed description of the methods
- File 2: Figure 1: Different phases of the TINY-3 study
- File 3: Interview guide TINY-3
- File 4: Tables demographic information participants

Supplemental file TINY-3 study, file 1 (Detailed description of the methods)

TINY-study & study design

This research is part of the Dutch study called Toward INdividualized care for the Youngest (TINY), initiated by three perinatal centers in the Netherlands: Erasmus MC Rotterdam, LUMC Leiden, and Radboudumc Nijmegen. While TINY-1 and TINY-2 studies focused on periviability guidelines, personalization, and parental values in decision-making surrounding extreme premature birth, TINY-3 focuses on the artificial amnion and placenta technology (AAPT) in extreme prematurity.[1-4]

As part of the TINY-3 study, a stakeholders meeting was performed following a guidance ethics approach.[5] This approach is not primarily focused on the question whether a technology is acceptable or not, but rather starts with the question how a technology can be given a responsible place in society. In the meeting, we discussed the actors who could be affected by the implementation of AAPT (and therefore should have a say in how and under what conditions the technology should be developed and used), the potential positive and negative effects that introduction of the AAPT could have and which values would be at stake with these effects.[5] Lastly, participants developed possible strategies to ensure the responsible development and use of the technology, specifically distinguishing options to promote key values by changes in the technology itself, options in the specific context in which the technology could be employed (e.g., organizational changes or agreements needed to promote key values) and options concerning what users of the AAPT themselves can do to promote responsible use.[5] With the input of this stakeholder's meeting, we performed focus group interviews and individual interviews to further explore and deepen the main findings of the stakeholders meeting:

I. Conditions and considerations regarding the human AAPT trials;
II. Considerations and concerns regarding the informed consent procedure during counselling and decision-making about the human AAPT-trials;
III. Ethical concerns regarding the care with the AAPT, such as inequality or slippery slope;
IV. The AAPT design, as potential solution for some of the unwanted effects of the AAPT.

This article presents the TINY-3 results on conditions for the first in human trials of the AAPT. The Scientific Committee of the Leiden University Medical Centre assessed the study protocol and waived the need for ethical review (reference: 23-3052).

Study participants

Participants were recruited through the TINY-database which consists of parents who experienced an (imminent) extremely premature birth and the Dutch patient association Care4Neo, social media (e.g., LinkedIn) and the researchers' networks. Inclusion criteria for this study were (1) working as HCP in perinatal care, or (2) being a parent who experienced an extremely premature birth before a gestational age of 28 weeks.

TINY-database

The TINY-database was created using Castor to include parents who experienced an imminent or actual extremely premature birth and were interested in participating in neonatology research.[1,4] Recruitment for the database was conducted through various channels, including the Dutch patient organization Care4Neo, the Dutch platform Stille Levens - kenniscentrum Babysterfte, physician networks, social media platforms associated with participating hospitals and researchers, and by contacting parents who had consented to further communication from prior studies (PreCo study - Prenatale Counselling in extreme prematurity, CODA study)[6,7].

To be included in the database, participants needed to meet one of the following criteria: (a) had an extremely premature birth between 23 and 26 weeks gestational age (GA) after 2010, or (b) experienced an imminent extremely premature birth between 23 and 26 weeks GA after 2010, but delivered at a later GA. Upon providing informed consent for inclusion in the database, all parents were asked to complete a brief online questionnaire. This questionnaire gathered demographic information about their experience with extremely premature birth (e.g., decision-making regarding intensive care or palliative comfort care, GA at imminent birth, GA at actual birth, and survival of the child) as well as their personal background (e.g., age, educational level, and native language).

Data collection

Focus group and individual interviews were conducted by members of the research team with various backgrounds (PhD-student, neonatologist, maternal-fetal-medicine specialist, ethicist, psychologist). The participants all granted informed consent before starting the focus group interviews.

An interview guide was developed based on the previously performed stakeholders meeting and the expertise of our multidisciplinary team. It comprised (I) general instructions about the technique and (II) open-ended questions corresponding to the themes that were found in the stakeholders meeting. It was emphasized that the discussion should focus on the current status of the development and the most urgent topic: the potential upcoming AAPT trial, rather than on possible applications of implementation in clinical care. During the interviews, prototypes developed by the PLS consortium were present to provide participants a clearer, more concrete understanding of what the technology could look like.

Data analysis

Results were analysed and coded independently by two authors (AB, RK) in Atlas.ti, using thematic content analysis following Braun and Clarke's guidelines.[8] This process included becoming familiar with the data, generating initial codes to develop a codebook, identifying patterns and themes within the data, reviewing and updating codes and codebook, and defining and naming the themes. The codebook and analysis were discussed within the team and adjusted in multiple rounds until agreement was reached.

Manuscripts TINY-3

The data collected from the interviews was extensive and multi-faceted, addressing various ethical considerations regarding the AAPT and the upcoming human trials. To thoroughly analyse and present these findings, we divided the data into four distinct manuscripts, each corresponding to key themes outlined in the interview guide and additional themes that emerged during our analysis.

Given the volume and complexity of the data, as well as the ethical implications raised throughout the discussions, four critical topic are separated into 4 manuscripts (see also *figure 1*) allowing for thorough examination of each critical theme. This approach ensures that fundamental ethical questions and concerns identified during the interviews receive the necessary attention and discussion.

The first paper focuses on the conditions surrounding the initiation of first-in-human trials.

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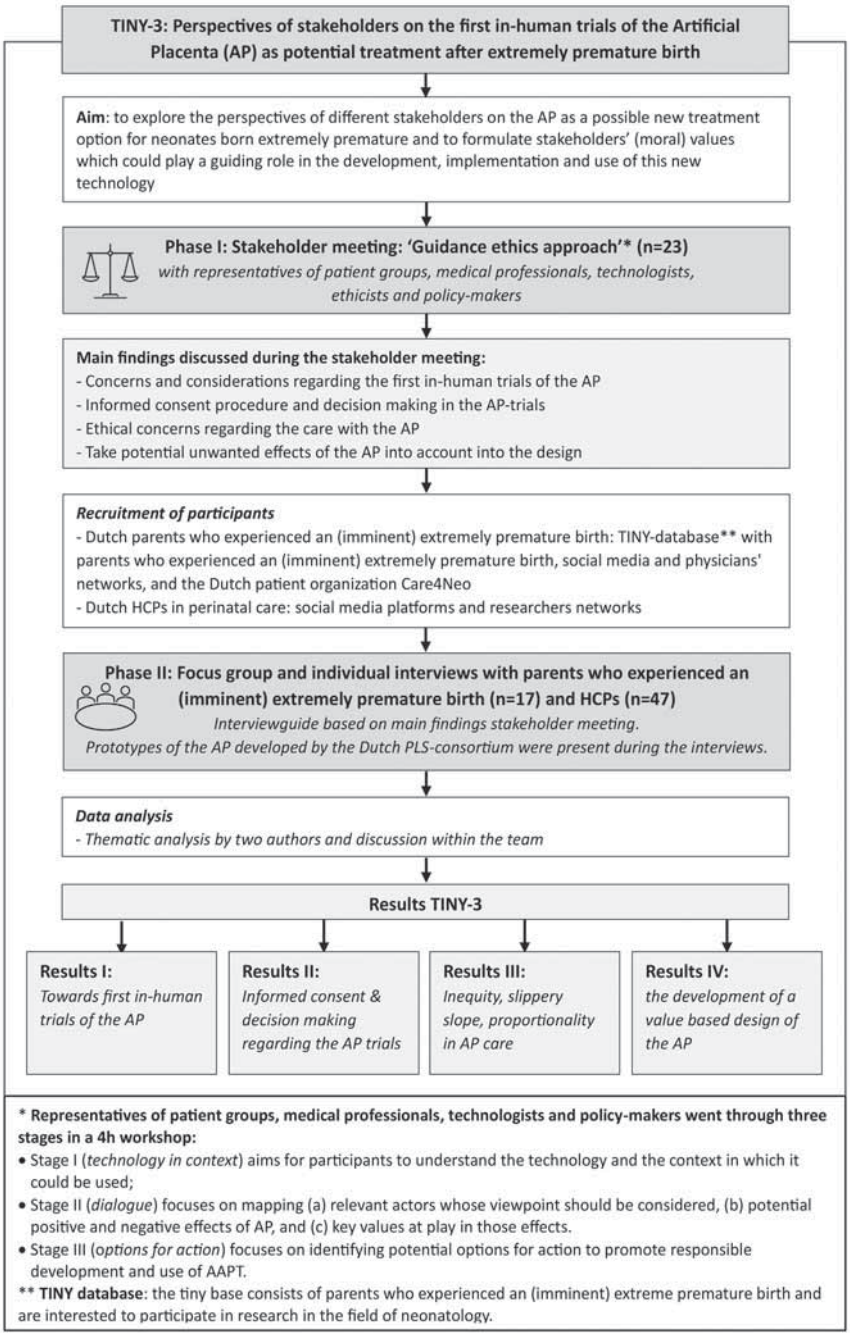
Supplemental file TINY-3 study, file 2 (Figure 1)

Figure 1 Different phases of the TINY-3 study



Supplemental file TINY-3 study, file 3 (Interview guide tiny-3 (translated from dutch to english)

Introduction:

- Explanation about how the focus group interviews will be performed, some regulations and practical matters
- Informed consent and demographic information
- Introduction to the topic: treatment of extreme prematurity and the current status of the development of the artificial amnion and placenta technology, which is the study phase before the first-in-human trials might start (i.e., before the first baby is placed in the artificial amnion and placenta technology). It can/may still be decided that this is not desirable.

1. ***Ethical Considerations for the Application of the Artificial amnion and placenta technology:***
    - Is the development of the artificial amnion and placenta technology a desirable advancement? Why or why not?
    - What are your primary ethical dilemmas associated with the application of the artificial amnion and placenta technology in humans? Why?
    - What ethical conditions must be met before first in human trials with the artificial amnion and placenta technology could be started?
        - What actions are necessary to fulfill these conditions?
2. ***Counseling and Decision-Making at the Individual Level***
    - Interview with parents:
        - What personal arguments, reasons, or circumstances might influence your decision to participate or not participate in such a trial?
        - What support or information would you need to make an informed decision about participating in the study involving the application of the artificial amnion and placenta technology in humans?
    - Interview with Healthcare Professionals:
        - What minimum standards do you believe counseling should meet to enable parents to make a decision about participating in the first study involving the application of the artificial amnion and placenta technology in humans?
3. ***Design of the Artificial amnion and placenta technology:***
    - Which aspects of current daily care for infants between 24-28 weeks of gestation in the NICU do you consider essential to retain in an artificial amnion and placenta technology?
    - What negative aspects of the current daily care for infants between 24-28 weeks in the NICU does the artificial amnion and placenta technology have the potential to improve or resolve?
    - What minimum conditions must the design meet before we can further develop or utilize the artificial amnion and placenta technology?

Present physical and digital prototypes.

- Do you still agree with the conditions you previously mentioned, or do you have any additions?

Supplemental file TINY-3 study, file 4 (Tables: demographic information participants)

Table 1A Demographic information of the healthcare professionals

Healthcare professionals	N=46
Specialty	
NICU nurse	16
Neonatologist	12
Nurse practitioner NICU	5
Maternal fetal specialist	4
Midwife / Physician assistant obstetrics	4
Obstetric nurse	3
Pathologist	1
Psychologist	1
Sex	
Female	38
Male	8
Age	
20-30	1
30-40	10
40-50	18
50-60	12
>60	5
Working experience	
1 to 5 years	7
6 to 10 years	5
11 to 15 years	8
16 to 20 years	4
21 to 25 years	10
25+ years	12
Any experience with premature birth in personal life or social environment	
Yes	11[a]
No	35

[a]*Experiences with premature birth: <28 weeks gestation (n=3), between 28 week-37 weeks gestation (n=5), or the gestation was unclear (n=3). The experiences were personal, in the family or with friends.*

Table 1B Demographic information of parents

Parents	**N**
Focus group interview with	
Mother	8
Father	5
Individual interviews with	
Mother	4
Father	1
Total parents interviewed	18
Participated	
Individual	12
As couple (father and mother)	3
Age in years	
20-30	3
31-40	9
41-50	5
51-60	1
Educational level	
Secondary vocational education	7
Higher professional education	7
University education	4
Experience with extremely premature birth	
>1 (imminent) extremely premature birth between GA 24+0-26+0	
Yes	2
No	13
Total cases	17[a]
Year of experience with extreme premature birth(s)	
2000-2008	2
2009-2016	4
2017-2024	11
GA at which extremely premature birth first threatened	
<23+0	1
23+0 – 23+6	6
24+0 – 24+6	5
25+0 – 25+6	2
>26+0	3
Birth between GA 24+0-26+0	
Yes	10
No, beyond 26+0	7
Multiple birth	
Yes	4
No, singleton birth	13

Table 1BContinued

Parents	N
Initial treatment decision between GA 24+0-26+0[b]	
Intensive care treatment	13
Palliative comfort care	2
Parent(s) did not make a treatment decision	2
Outcome of the premature birth[c]	
Survivor(s) (incl multiples)	12
Deceased	5
Self-reported consequences of extremely premature birth	
No consequences observed	8
Any	4

[a] *Seventeen cases of extreme premature birth includes two couples/individual parents experienced more than two (imminent) extremely premature births and 15 couple/individual parents experiencing one (imminent) extremely premature birth. Extremely premature birth of a multiple is recorded as one case.*
[b] *This includes parents who initially opted for palliative comfort care as the treatment plan until 26+0 weeks gestational age, but whose infant was born after 26 weeks.*
[c] *The outcome of premature births was categorized as either survivor or deceased accounting for both singleton and multiple births. For instance, the survivor(s) outcome encompasses singletons who survived or multiple births where both children survived*

Chapter 10

English summary and general discussion

English summary and general discussion

This chapter summarizes the studies conducted within this thesis structured into two sections and provides a comprehensive discussion of their results. In the general introduction, we introduced (I) the context of extreme premature birth, (II) explored the concepts of shared decision-making and value clarification at the limit of viability, (III) and discussed one of the newest developments in perinatology: artificial amniotic and placental technology. Additionally, we outlined the objectives of this thesis:

1. To explore which values are considered important in treatment decisions focusing on neonatal early intensive care or palliative comfort care at the limit of viability according to adults who are born extremely premature and experienced parents;
2. To explore the different perspectives of varying stakeholders on the development of artificial amnion and placenta technology with a specific focus on the ethical concerns and considerations surrounding the first in-human trials in the context of its intended purpose: providing treatment for extremely premature births.

English summary

This thesis is structured into two sections. An overview of the TINY-studies is recorded in *box 1*.

Box 1: An overview of the TINY-studies

Part I Values in decision-making at the limit of viability

TINY-1 study | Perspectives of extremely prematurely born adults on what to consider in prenatal decision-making: a qualitative focus group study

TINY-2 study | Voices of experience: what parents teach us about values and intuition in periviable decision-making

Part II The artificial amnion and placenta technology as potential treatment for extremely premature infants

TINY-3a | Informing the Responsible Design of First-In-Human Trials for Artificial Amnion and Placenta Technology

TINY-3b | Healthcare professionals' and parental perspectives on human artificial placenta technology-trials: counselling and informed consent

TINY-3c | The ethical concerns of Dutch perinatal healthcare professionals and experienced parents regarding artificial amnion and placenta technology

Part I: values in decision-making at the limit of viability

Part one, which consists of three chapters and two intermezzo's, focuses on values that are considered important in decision-making between early intensive care and palliative comfort care at the limit of viability. Chapter 2 comprised a scoping review of the existing body of literature aiming to show what is known in literature on parental values considered

important in decision-making at the limit of viability and to identify gaps in the current body of literature. An analysis of 17 articles, which was performed together with parents of an extremely premature infant, offered insight into the most common values underlying parental decisions. Overall, the results were complex and multi-layered with some themes reflecting on balancing the factual information on outcomes for infants and families, as well as numerous underlying and potentially conflicting values. Other themes reflected more on preferences regarding the process, such as the desire to do everything possible, or reflect feelings or intuitions, such as the instinct to save the child.

In Intermezzo A, the parents who co-authored our scoping review shared their personal experiences with extremely premature birth. They provided insights into the difficult decisions they faced, the factors they deemed important, and the pivotal role of emotions and intuition in their decision-making process. Their perspectives were part of the inspiration for the interview guide used in the interviews of the TINY-2 study.

Chapter 3 reported the findings of the TINY-1 study, which explored the perspectives of adults who were born extremely premature. This chapter presented data from four focus group interviews with 23 participants, exploring their perspective on factors to consider during treatment decisions focusing on neonatal early intensive care or palliative comfort care at the limit of viability. The findings underscored the importance of addressing expectations and uncertainties surrounding individual prognosis. Furthermore, emphasis was put on considering the long-term consequences on both the premature person themselves, as well as on their family. Additionally, the study revealed that the current follow-up care and support for infants and adults born extremely prematurely was not experienced as sufficient, with many participants expressing a desire for more specialized clinics and programs tailored to their unique needs. The group described extremely premature birth as “a lifelong diagnosis” highlighting the enduring impact on their health and well-being.

In light of these findings, the TINY-1 study showed the need for increased awareness and attention to the group adults born extremely prematurely. To amplify this message, a collaborative effort with participants resulted in an article for Medisch Contact (Intermezzo B). The article proposed several key initiatives, including personalized follow-up care, alternative outcome measures, further research into long-term consequences, the integration of birth history into all patient records, and the establishment of a national expertise centre for the consequences of extremely premature birth.

Chapter 4 presents the results of the TINY-2 study, a qualitative interview study with parents who experienced an actual or imminent extremely premature birth. A total of nineteen interviews were performed. Considerations and values of parents mostly revolved around the infants’ future and the impact on the whole family. They acknowledged both intuitive and rational aspects of decision-making, with more emphasis on intuition and gut feeling. Furthermore, strategies to help parents formulate their values during counselling were

provided, such as examples of guiding questions and the incorporating of value-clarification strategies into decision aids. Parents highlighted conditions that could facilitate this process, including clear and unbiased communication of information, some time to reflect on the information and the decision to be made, and a multidisciplinary approach involving the appropriate professionals.

Part II: perspectives on the development of an artificial amnion and placenta technology

Part two focuses on ethical considerations and concerns regarding the development of artificial amnion and placenta technology. This section consists of five chapters and one intermezzo, aiming to explore these issues through diverse perspectives. Insights are drawn from a review of the existing literature, discussions with various stakeholders, and interviews with two key groups: parents who have experienced actual or imminent extremely premature births, and healthcare professionals working in perinatal care.

Chapter 5 presented the findings of a systematic review examining the ethical debate surrounding artificial amnion and placenta technology. Analysis of extracted data from the 45 included ethical articles were divided into three central themes. The first theme, "foundational ethical issues," explored differing perspectives on whether the subject supported in the artificial amnion and placenta technology should be regarded as an infant or a new moral category altogether. The second theme, "reproductive ethics issues," addressed the potential of artificial amnion and placenta technology to either expand or constrain reproductive choices, highlighting concerns about societal pressure to use it in healthy pregnancies or as an alternative to abortion. The third theme, "research ethics issues," centered on the ethical challenges related to selecting participants for the first in-human trials of this technology. The review concluded that existing ethical discussions predominantly focus on the potential application of artificial amnion and placenta technology in contexts such as alternatives to abortion or use in healthy pregnancies, rather than its primary intended purpose: providing treatment for extremely premature births. Furthermore, the results showed that empirical research was lacking in the ethical literature. This highlighted a need for empirical data with stakeholders and a more targeted ethical analysis on its use within neonatal and perinatal care.

Chapter 6 described a commentary written in response to the review by De Bie et al., titled "Ethics considerations regarding artificial womb technology for the fetonate".[1] In this commentary, we proposed enriching the ethical debate on artificial amnion and placenta technology by incorporating a broader normative framework, such as the capability approach. We also suggested to use the Guidance Ethics Approach for a societal dialogue about artificial amnion and placenta technology, which integrates empirical data into ethical discussions to promote responsible innovation.

As initial step in the TINY-3 study, we organized a Guidance Ethics Workshop to gather empirical data and involve stakeholders in the ethical evaluation of artificial amnion and placenta technology. As the results of this workshop, a report (intermezzo C) was written in which we identified key individuals and groups whose perspectives should be included, the potential impacts of using the technology in its intended context, and the values at play. Participants also developed options for action to support the responsible development and implementation of the technology. These strategies were categorized into the three approaches as part of this method: (1) modifying the technology itself to address ethical considerations (*ethics by design*), (2) adapting the broader environment in which the technology is used (*ethics in context*), and (3) empowering individuals who interact with the technology to engage with it responsibly (*ethics by user*). Key themes identified were (I) conditions and considerations for conducting first in-human trials of the artificial amnion and placenta technology, (II) concerns regarding the informed consent process during counselling and decision-making about clinical trials for the technology, (III) ethical concerns related to the eventual clinical implementation of artificial amnion and placenta technology, such as issues of inequality and the risk of unintended consequences, and lastly (IV) the design of this technology as potential solution for some of the unwanted effects of artificial amnion an placenta technology.

Building on the outcomes of this workshop, we conducted focus group discussions and individual interviews with experienced parents and healthcare professionals working in perinatal healthcare to further explore the key issues raised during the Guidance Ethics Workshop. These interviews revealed several important findings, which are discussed in Chapters 7-9 for the first three themes. The fourth theme -focusing on the design of the artificial amnion and placenta as a potential solution to mitigate some of its unintended effects- is not included in this thesis.

Chapter 7 presented the findings of the TINY-3a study, which explored the key stakeholders' considerations for designing the first human trials involving artificial amnion and placenta technology. Key considerations identified in the study were to optimizing the animal model, to define the primary goal of the first-in-human trial, to carefully select the research population, to establish stop criteria, success criteria, and outcome measures, to determine the role of parents during the trials, and to develop comprehensive trial protocols that addressed logistical challenges.

Chapter 8 presented the results of the TINY-3b study, which focused on the stakeholders' considerations regarding counselling and the informed consent process for participation in first in-human trials of artificial amnion and placenta technology. The study highlighted several key themes, including the stakeholders' perspectives on the moral and legal status of the subject being treated in these trials, the involvement of the pregnant person as the first trial participant, and the terminology used to describe the technology. Additionally, the study discussed the complexities of the informed consent process and counselling,

with particular emphasis on parental hope. The themes were interconnected, with the moral and legal context of the trials influencing how counselling and informed consent should be approached.

Chapter 9 presented the results of the TINY-3c study, which addressed the stakeholders' primary ethical concerns related to the clinical translation of artificial amnion and placenta technology to the standard of care. The following concerns were discussed: the potential impact of the technology on viability, the risk of overstepping natural limits, the balance of risks and benefits, and issues related to resource allocation, equity, and access to care.

General discussion

The following chapter reflects on the findings presented in this thesis, focusing on two key areas: decision making at the limit of viability and perspectives on the development of artificial amnion and placenta technology.

Shared decision-making

Shared decision-making is widely seen as the preferred approach for preference sensitive medical decisions when no single best treatment option is optimal.[2,3] While various models of shared decision-making exist, we recommend the Stiggelbout model, which includes four steps[3]: (1) the healthcare provider informs the patient that a decision must be made and emphasizes the importance of the patient's input, (2) the available options are discussed, including the advantages and disadvantages of each option, (3) the provider explores the patient's preferences and values, and lastly, (4) the provider and patient decide whether to make, defer, or postpone the decision.[3] In line with this shared decision making model, counselling parents at the limit of viability includes providing information, exploring parental values, hopes, and preferences, preferred decision-making roles and integrating these with the available options: intensive care treatment or palliative comfort care.[4,5]

Research showed that most Dutch parents and healthcare professionals consider shared decision-making to be the right approach for treatment decisions focusing on neonatal early intensive care or palliative comfort care at the limit of viability.[5,6] Similarly, participants in the TINY-1 and TINY-2 study also regarded shared decision-making as the most appropriate approach while emphasizing a tailored approach.

Part of a more tailored approach may be to better implement the last step of the Stiggelbout model: exploring whether the patient has the desire to make the decision.[3] Parents should be encouraged to participate in decision-making to the extent they prefer, including the option to abstain. This part of the shared decision-making process is crucial, as it ensures that the decision is made in a way that respects the parents' preferences, and desired level of involvement.[7] Parental preferences regarding the extent of involvement in decision-making should not be considered static; rather, they are dynamic and subject to change

over time. These preferences require careful and continuous attention to ensure they are appropriately understood and respected.[7] Even if the parent chooses to defer the decision, the prior steps (such as exploring values) remain just as important. The ultimate decision can still be shaped by the parent's values, preferences, and hopes. For some parents making such complex decisions may feel outside their control or beyond their capacity, and they may prefer that the physician, or even a higher power, make the decision on their behalf. With deferring the decision, parents may want to defer responsibility of the decision to prevent feelings of regret if the outcome does not align with the expectations.

In the context of human trials with artificial amnion and placenta technology, informed consent is essential.[8] Introducing clinical trial participation could be the ideal setting for shared decision making, aligning the decision with parental preferences.[9] Unlike the uncertainty in extreme preterm birth, which primarily involves individual prognostic variability, this novel technology presents significant uncertainty, as even group outcomes are not yet available. While such uncertainty makes trial participation inherently preference-sensitive, the legal requirement for free, informed consent may place it beyond the scope of shared decision making.[9,10] As informed consent safeguards the patient's autonomy by ensuring individuals fully understand the trial's purpose, risks, and benefits, rather than engaging in a collaborative process to determine the best personalized treatment option.[10] Nevertheless, research on clinical trials indicate that the exploration of values and preferences is valued.[11] This suggests that shared decision making could be a useful approach for the decision regarding participation in trials of artificial amnion and placenta technology.

Important values

Part I of this thesis presented several studies (TINY-1 and TINY-2 study) on personal values, beliefs, and preferences that were considered important in treatment decisions focusing on neonatal early intensive care or palliative comfort care at the limit of viability. Most emphasis was put on considering the long-term consequences for the infant and the impact of an extremely premature born infant on the family.

Counselling at the limit of viability usually involves informing parents about survival rates and potential long-term consequences. However, research indicates significant variability in neonatologists' prognostic predictions for similar cases, likely due to different interpretations of data, limited precision in prognostication, and varying attitudes regarding disability.[12-15] The way physicians communicates information about prognosis may shape parents' values, preferences and ultimately their decisions.

The information provided during counselling may not always align with what matters most to the individual parent.[16] Parents may prioritize specific considerations related to their infant's future.[16,17] For example, our participants had varying interpretations of 'quality of life' varying from the ability "*to be and act like others*", to "*playing sports*", "*having relationships*" or "*living independently*". While these subjective interpretations of quality of life may

not serve as strict outcome measures, they provide valuable insights that can help translate certain outcomes into contributions that align with what parents consider important.

In addition to addressing physical consequences, counselors should also discuss the psychological and social challenges that extremely premature infants may face, emphasizing that these can persist beyond childhood. Parents should be encouraged to consider these consequences and the impact it may have on the family while being assured that it is both valid and acceptable to take this into account.

The challenge for counselors is to present prognostic information about the physical, psychological, and social consequences in a neutral way, and subsequently interpreted this information together with parents to what matters most to them. Additionally, we advise counselors to address the impact of an extremely preterm birth on the family. While it is important to provide information on these topics, we recognize that counselors also have to navigate the limited time available and the emotional and cognitive load parents face during this stressful period. So, prioritizing the most critical information is essential, as it is neither feasible nor effective to discuss every possible detail. A decision aid, such as www.keuzehulpvroeggeboorte.nl, can serve as a valuable support tool in facilitating this process.[5]

The values of our participants found in Part I of this thesis highlight the importance of long-term physical, social, and psychological outcomes for their child, and while still far from realization, artificial amnion and placenta technology may hold potential to address these concerns in the distant future. However, whether this can be achieved remains uncertain.[18-20] Parents expressed concerns about the lack of long-term data in the context of potential human trials, as such outcomes are critical and often guided the treatment decision in their own experience with extreme premature birth. Addressing this requires a robust follow-up framework if the technology is studied, including comprehensive outcome measures in early human trials to better understand its effects. However, current follow-up is already lacking, which would be essential to compare outcomes of this technology. So, it may be important to improve the current follow-up first, before developing a framework for this new technology. Potential long-term consequences for the infant also extend to impacts on the family, a concern raised in discussions about this technology.

Trial of therapy

In the TINY-1 and TINY-2 study, participants discussed giving the child a chance and initiate early intensive care treatment, with redirection of care to palliative comfort care if a poor outcome is anticipated. Norwegian researchers also described this option of framing initial intensive care as a "trial of therapy", emphasizing that the expected quality of life can be reevaluated and that therapy may be withdrawn later if deemed appropriate.[21] This approach may provide comfort to parents, as it feels less definitive and more flexible than committing to intensive care and acknowledges their concerns about quality of life.[5] However, some healthcare professionals view continuous reevaluation of treatment

effectiveness as an inherent aspect of all intensive care rather than a distinct or optional strategy, making the concept of a trial of therapy redundant. This perspective may be particularly characteristic of Dutch healthcare culture based on national cultural and societal values.[6,22,23] Regardless of whether this is a semantic discussion, the framing and communication of these decisions, including the choice of language, are crucial in supporting parents to articulate what matters most to them.

The importance of hope

In addition to values and religious or spiritual beliefs, existing research and this thesis demonstrated that hope played a role in guiding decision-making at the limit of viability.[24-27] Previous studies have shown that hope allows parents to navigate uncertainty, enabling them to make decisions that align with their values and beliefs.[28,29] At the limit of viability, where outcomes are highly uncertain and the stakes are profound, hope often centres around the potential for a positive outcome despite the statistics.[30] Part 2 of this thesis (TINY-3 studies) suggests that artificial amnion and placenta technology may further amplify parents' sense of hope. In contrast to current NICU treatments, this technology lacks existing statistical data, which might temporarily alleviate some fears when risks would have been known. This raises the risk of "therapeutic misconception", where parents may overestimate the potential benefits of artificial amnion and placenta technology or misconstrue experimental treatments as proven therapies.[31,32] While hope is invaluable, counselling in both situations must carefully address the realistic chances for the infant to prevent false expectations or misunderstandings.

Intuition in decision-making

The role of intuitive processes in decision-making is gaining increasing interest in the field of healthcare.[33-35] An increasing number of theories on decision making assume both intuitive and deliberative decision-making processes play a role. Intuition is an unconscious process, although difficult to quantify with valid and reliable measures, often described as 'gut feeling'.[36] In contrast, deliberative mental processing is more explicitly analytic, slow, and effortful.[37] Both processes are not mutually exclusive, and research shows both are used.[38] Intuitive decision-making can lead to quicker decisions and may be more effective in situations where time is limited, as it might help in integrating large amounts of information, but it can also be prone to biases and errors. On the other hand, deliberative decision-making may be more thorough in formulating preferences potentially leading to more congruent decision. However, explicit deliberation can also be time-consuming and can cause negative emotions to intensify.[35]

As our TINY-2 study showed, parents differ in how they wish to make complex decisions, with a minority of the participating parents -mostly men and couples that opted for palliative comfort care- viewing their decision as rationally made. In the TINY-3 studies, parents initially saw the technology as a source of hope, leading some to consider participation primarily for their child's potential benefit. However, as they gained a deeper understanding

of the risks and benefits, including those that affect the mother, some parents' perspectives shifted.

A useful approach was recently suggested by Geurtzen & Wilkinson.[39] They suggest to facilitate both intuitive and rational decision-making, explore specific health beliefs, and help refine internal mental models. To evaluate the role of intuition, they also suggest to gently challenge a parental preference to determine if it is stable and well-informed. This can be done by asking whether the preference truly aligns with the parents' core values, encouraging them to pause judgment until they have a full understanding. Clinicians can also suggest that parents' preferences may evolve as they learn more about the risks and benefits, allowing space for uncertainty, and helping to distinguish short-term emotional reactions from long-term outcomes.[35,39-41]

Value clarification – a doctor's task?

One parent in the TINY-2 study stated "*I don't know if physicians should [help parents clarify their values], they are not trained to do so*", reflecting a common concern among parents about the capability of physicians to facilitate value clarification during prenatal counselling regarding extreme premature birth. A multidisciplinary approach involving professionals specifically trained to explore values was one of the suggestions to improve value clarification. This raises important questions about whether physicians are truly unprepared for this role, whether they should be equipped with the necessary skills, or whether this responsibility might be better suited to (or shared with) other disciplines. Effectively addressing these challenges requires integrating both the ability to explore patients' values and the medical knowledge about their conditions. Physicians are uniquely positioned to seamlessly weave medical information into conversations about values, facilitating a holistic approach to care. While specialists like spiritual counselors excel in exploring values and finding meaning, they may not easily integrate medical information into the discussion. Moreover, professionals such as spiritual counselors are not always available, particularly during urgent situations or late at night. This underscores the importance of equipping physicians with the skills to navigate these nuanced conversations effectively. Lastly, families may have strong preferences about who they want to guide them in these decisions—whether it be the obstetrician they have known throughout the pregnancy, the neonatologist with specialized insights into the baby's condition, or professionals like a spiritual or social counsellor who can provide emotional and existential support.

Given the centrality of value clarification in treatment decisions, we believe it is imperative that physicians develop the skills to facilitate this process. Preference-sensitive and value-laden decisions are not confined to neonatology or obstetrics but are prevalent across all fields of medicine. However, many physicians lack the training, confidence, or inclination to prioritize value exploration in patient conversations.[40] While shared decision-making is gaining prominence in medical education, the specific focus on helping patients articulate their values remains underdeveloped. Integrating training on value clarification into the

medical curriculum would enhance this critical competency, ultimately improving patient care across disciplines.[42]

Eliciting the patient's values is part of meaningful conversations between clinicians and patients, laying a foundation for shared decision-making and patient-centered care. In the context of imminent extreme premature birth, the relationship between patients and clinicians becomes particularly crucial, as trust is essential. Regardless of the treatment decision, engaging with parents to understand what matters most to them and their family is vital for establishing a productive relationship between parents and physicians. As demonstrated in De Proost's thesis, parents described personalization in periviable care as "building a relationship with healthcare professionals" and "feeling seen and heard".[43] Physicians should be genuinely curious about the lives of their patients, what is important to them, and what they - in the context of neonatology or paediatrics - envision for their child and family.

Technical state of the art and its effect on neonatal care

High technological care at the limit of viability is rapidly redefining the boundaries of neonatology.[44,45] As advancements in neonatal intensive care become more refined and widespread, there is a growing tendency to normalize what once was considered extraordinary and high technological care.[46-48] This shift reflects the interplay of technological determinism—where technological capabilities drive clinical practices—and the technological imperative—the compulsion to use technology simply because it exists.[49]

This thesis explored the different perspectives of stakeholders on artificial amnion and placenta technology described in the TINY-3 studies in part II. Though currently seen as highly technological and experimental—and often associated with science fiction—history suggests that, if proven safe and effective, this new technology could eventually become as normal as ventilators and surfactant therapy. However, this potential normalization risks overlooking the ethical complexities and potential futility of some interventions, particularly when long-term outcomes remain uncertain. Neonatal care must balance the promise of cutting-edge technology with careful value clarification for families and society, to avoid assumptions that high-tech treatments are always the best option.

Despite the rapid advancement of neonatal technologies, there remains a significant gap in our understanding of the long-term outcomes into adulthood for infants born at the limit of viability. Given this gap and the remaining challenge for effective long-term follow-up in current practices, it is essential to ensure that emerging innovations, such as artificial placenta systems, integrate robust mechanisms for monitoring and evaluating long-term outcomes. Healthcare professionals frequently prioritize the development and implementation of new interventions, driven by a commitment to innovation and improving immediate outcomes. However, this drive for progress often overshadows the equally important need for strong post-discharge care and monitoring, which are crucial for assessing and

improving long-term outcomes. This also raises critical questions about whether the focus should prioritize innovations with their the follow-up, such as artificial placenta systems, or emphasize improving current long-term follow-up care.

Global health perspective

In the context of global health, neonatal intensive care represents a critical area of focus due to the significant burden of preterm births, the associated complications worldwide and the significant disparities in access to specialized care between low- and middle-income countries and high-income countries.[50] The disparity in healthcare infrastructure contributes to differences in mortality and morbidity rates, as well as the interpretation of the concept of viability. Advancements in NICU care have led to remarkable improvements in survival rates, however often these advancement are particularly implemented in high-income countries. The increasing ability to save premature infants in these countries together with the disparity in access to new innovative technologies across low- and middle-income countries highlights a global inequity. This divide prolongs a dual burden: resource-rich settings must grapple with the ethical implications of prolonging life without assured quality, while resource-limited settings remain constrained by basic neonatal care deficits.

Furthermore, the focus on viability-centric innovations in high-income settings risks diverting attention and resources from scalable, cost-effective interventions—such as kangaroo care, infection prevention, and nutrition support—that could have a broader impact on global neonatal survival. As NICU care continues to advance, it is imperative to critically evaluate its global implications, ensuring that innovation not only extends viability but also promotes equitable health outcomes worldwide.

Translating insights to broader applications (ethical, practical, research)

In this thesis, it became clear that peer support is often inspiring and important for groups of patients who feel unseen and whose problems lack recognition, such as our group of adults who are born extremely premature (TINY-1). While not everyone feels the need to connect with others sharing their diagnosis, for some, this connection is an important part of their journey.

Furthermore, while we studied a specific setting within the neonatology context, our recommendations extend beyond this specific setting. They can be applied to other settings with grey-area decisions and to other fields of medicine, such as paediatric intensive care or general paediatric wards. Every healthcare professional should have the skills to help their patient explore and formulate their values and ask the patient or surrogate decision-maker how and if they want to make the decision.

Our structured approach to emerging technologies that may influence life and death, may serve as a valuable blueprint. This includes early-stage stakeholder involvement in and

the use of the Guidance Ethics Approach. Ensuring ethical and responsible development requires the active involvement of stakeholders throughout the process.

Reflections on this thesis / strengths and limitations

This thesis has several strengths but also some limitations. A key strength of our work is the involvement of a diverse range of stakeholders in all the studies. Our multidisciplinary team, which included neonatologists, a maternal-fetal medicine specialist, ethicists, a psychologist with a focus on medical decision-making, PhD students, and representatives from the Dutch patient organization Care4Neo, members of the PLS consortium as well as parents of extremely premature infants, played a crucial role in strengthening the analysis and interpretation of the results. The involvement of Care4Neo was very valuable, as their input played a crucial role from the early stages of protocol development to the writing of the manuscript. They provided insights on addressing sensitive topics, adjusting materials for our participants, interpreting results, and ensuring that the perspectives of the parents were clearly represented in the articles. The input from members of the PLS consortium was also very valuable, as their expertise contributed to the interpretation of the results. Furthermore, they provided prototypes of the artificial amnion and placenta technology they had developed, which served as a starting point for discussion during the interviews. Additionally, one of the strengths in our methodology was purposive sampling to include a diverse group of participants, facilitated by the development of a database for parents who had experienced the birth of an extremely premature infant. Participants were selected aiming for variation in personal demographics (age, education, geographic location in the Netherlands) and specific experiences with extremely premature births, such as gestation at birth, outcomes, and the decisions made at the limit of viability.

However, there are several limitations to note. First, the results can be context-specific and may be limited to the Dutch setting. However, our results also provide learning points that hold cross-cultural relevance, offering insights applicable across diverse cultural contexts. Second, despite efforts to recruit a diverse sample through purposive sampling, there was an underrepresentation of individuals who identified as religious or who came from non-white ethnic backgrounds which is a known problem in this research area. Both cultural and religious factors are crucial to understanding the values and decisions of individuals in these contexts. Moreover, the TINY-1 study, which included adults born extremely prematurely, did not capture the perspectives of individuals who experienced severe consequences from their extremely premature birth. The study's methodology required participants to have a certain level of cognitive functioning to participate in focus group interviews. As a result, the study excluded individuals whose impairments might have limited their ability to express themselves in this format. Nevertheless, the perspectives of survivors with various outcomes from extreme prematurity were still represented, as the majority of the participant experienced some form of physical, social, and psychological consequences. Lastly, during the TINY-3 studies, it proved challenging for our participants to distinguish between a trial setting employing artificial amnion and placenta technology

and a care setting incorporating this technology, which may have influenced the results. However, this also highlights how closely related these contexts may be, particularly from the perspective of parents.

Future perspectives

Education in Value clarification

Future research could examine whether healthcare providers explore parental values during counselling, identify barriers and facilitators, and develop strategies to address barriers while strengthening facilitators. Insights could guide educational programs to support providers, extending beyond viability decisions to other hospital settings. Integrating this into medical training, with a focus on continuous development throughout the path to becoming a medical specialist and beyond, could help future doctors and specialists navigate value-laden decisions and engage effectively with patients.

Outcome measures

Current outcome measures could be expanded and more closely aligned with what matters to parents. Collaborating to define universally accepted outcome parameters that consider the perspectives of physicians, infants, and families is crucial for both research and counselling.[17] This dissertation shows that more research is needed on patient reported outcomes measures. Additionally, there is a need for data on long-term outcomes for adults born extremely prematurely. For example, the very recently granted proposal on patient reported outcome measures in prematurely born adolescents is a promising project in this field.[51]

Importance of follow-up and expertise centrum

The follow-up in neonatal care should be extended to identify and address long-term developmental and health challenges in infants who are born extremely premature. Currently, the guideline advises follow-up until 8 years of age for extremely preterm infants. However, in practice, this is not fully implemented across all perinatal centers, and follow-up in some centers is limited to 5-6 years. So far, the barriers appear to be mainly financial and related to physicians, but gaining more insight into these barriers, increasing awareness and knowledge may help to expand the follow-up period. Long-term follow-up – at least until adulthood – is essential not only for assessing survival and morbidity rates, but also for the timely recognition of health issues and the activation of appropriate care and up-to-date counseling based on recent data. Furthermore, it is essential for evaluating whether treatments, such as artificial amnion and placenta technology, lead to improve outcomes. Establishing a nationwide expert center on middle and long-term effects of extremely premature births may provide valuable guidance and resources for patients, parents, and healthcare professionals, ensuring comprehensive care throughout the life of the children and adults who are born extremely premature. Such a center could offer specialized knowledge, foster collaboration, can assist in finding and arranging the appropriate care

and may also provide advice on referrals, hopefully resulting in improved quality of life of patients and their families.

Development of artificial amnion and placenta technology

Ongoing research is needed in the field of artificial amnion and placenta technology, both in terms of technological and safety aspects, as well as ethical and legal considerations. Given the concerns in the Netherlands and the lack of long-term data or the current status, it may be reasonable to closely monitor international developments while carefully weighing the national PLS objectives. These should be made sensitive to the findings of this thesis.

Update decision-aid extreme prematurity [Keuzehulp Vroeggeboorte]

The Dutch decision aid 'Keuzehulp Vroeggeboorte' was developed based on the PreCo studies, but before the start of this thesis.[5] At that time, knowledge on actual parental values and preferred value clarification was somewhat limited. With the next update of this decision aid, insights from this research should be incorporated into the decision aid.

Development of Guidelines

Guidelines in general should allow for flexibility in situations that are not strictly black-and-white, presenting potential trade-offs and allow time for encounters. This approach challenges current guideline development methods, which are based on the GRADE level of evidence, and may require us to rethink how we create and implement these frameworks. The input from this dissertation could be considered in the upcoming revision of the current guideline.

Financial resources

Preference sensitive treatment discussions require time and thus money, but the potential benefits are significant. Properly aligning care with patient values and avoiding over-treatment could lead to more appropriate and efficient healthcare. In the long term, this approach may result in better resource allocation and improved health outcomes.[40] Healthcare systems should facilitate financial resources to invest in the implementation of conversations about values and preferences.

My role as a young medical doctor and qualitative researcher

In this thesis, different approaches of qualitative research were used. As a qualitative researcher, you are an instrument of the research, and your own biases inevitably influence the process.. The data collected in the research can directly shape and alter the perception of the researcher(s).

As a young medical doctor and a researcher in the field of periviable decision-making, the author of this thesis had a dual role. The interviews of the TINY-1 and TINY-2 study were performed together with Lien De Proost, an ethicist and researcher. For the TINY-3 study, the focus group interviews were always performed in a team of minimal two persons (moderator and observer), with background ranging from young medical doctor, maternal fetal medicine specialist, neonatologist or ethicist.

Dual role

Balancing the dual role of young doctor and researcher came with some opportunities and challenges. As a medical doctor, I had the advantage of understanding complex medical contexts, which helped me empathize with participants and interpret nuanced data. Furthermore, my background and training as a medical doctor often helped me connect with participants, particularly when discussing medical or emotional topics. However, this dual role also posed challenges, such as the potential for respondents to perceive me more as a healthcare provider than as a researcher. At times, my role as doctor influenced how participants engaged with me and my fellow interviewer. An example of this is that during discussions of more medically related topics, participants tended to direct their attention toward me, whereas, when ethical subjects were addressed, they often turned first to my co-interviewer, the ethicist. Importantly, I think my dual role allowed me to gain deeper insights into participants' lived experiences, ultimately enriching the study's findings.

Lessons learned

One of the most valuable aspects of this research was learning from every interview with the parents I spoke to. In the following paragraphs, I highlight three key lessons I have gained and will apply in my future work as a young doctor; however, these are by no means the only insights I have learned from this research.

First, this experience underscored the importance of reassurance—not just in research but also in clinical interactions with patients and families. Letting people know that their thoughts and opinions matter, and that there is no judgment, fosters a sense of trust and openness. Many parents found it intimidating at first to share their experiences, expressing uncertainty about whether their responses were "right" or aligned with what I was seeking. Reassuring them that there were no "correct" answers and emphasizing my curiosity about their genuine perspectives helped create an open dialogue.

Another key lesson for me was how essential it is to approach every conversation with honesty and sensitivity. Being transparent—such as admitting when I did not know the answer to a question—helped build trust. Parents often shared that the healthcare providers they most appreciated were those who were honest and made them feel seen and heard. They valued small but meaningful acts of kindness, like celebrating milestones for their child or simply serve them a good cup of coffee. These reflections reinforced my belief in the power of empathy and attentiveness, both in research and in medical practice.

Lastly, a profound lesson was the importance of curiosity—not just curiosity about the outcomes of research, but about understanding what truly matters to patients and their families. Asking thoughtful "why" questions without making participants feel interrogated or misunderstood is essential. I learned to avoid projecting my interpretations onto their answers, as their experiences could diverged from my assumptions. This open-mindedness and genuine interest in their stories allowed me to uncover deeper insights and enriched the research findings.

Concluding remarks

This thesis underscores the crucial role of values in decision-making, particularly in the context of healthcare and the development of new technologies. Parents seek an active role in the exploration of these values when making critical decisions regarding the care of their infants, especially in preference-sensitive and time-critical situations. As we navigate the complexities of medical advancements, it is clear that values should not be merely an afterthought, but an integral part of the decision-making processes. Education for healthcare providers must, therefore, emphasize the exploration of parental values, equipping professionals with the skills necessary to foster value-centered decision-making in varying situations.

Furthermore, the importance of long-term follow-up care for infants born at the limit of viability cannot be overlooked. The lack of comprehensive data in this area highlights the critical need for better follow-up, and the importance of research that bridges technological advancements with an emphasis on sustained, longitudinal care. Such efforts are necessary to ensure that the development of new technologies is accompanied by a commitment to the well-being of these vulnerable infants throughout their lives.

Finally, this thesis serves as the beginning of a broader societal dialogue in the context of artificial amnion and placenta technology. Engaging all relevant stakeholders across different phases of care and decision-making is essential to ensure that all important voices are heard. This work is just the beginning, we hope to have contributed to the field of decision-making and artificial amnion and placenta technology. Value-centered care should be ensured in neonatal care.

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Chapter 11

Appendices

Nederlandse samenvatting

Er is sprake van extreme vroeggeboorte als een baby vóór 28 weken zwangerschap wordt geboren. Dit brengt medische en ethische uitdagingen met zich mee. Rond de grens van levensvatbaarheid staan ouders en zorgverleners voor moeilijke beslissingen, één van deze beslissing gaat over het al dan niet starten van intensieve behandeling na een geboorte tussen de 24 en 26 weken zwangerschapsduur. In dit proces speelt gezamenlijke besluitvorming een centrale rol: ouders en professionals verkennen samen wat voor hen de beste beslissing is, rekening houdend met medische informatie én persoonlijke waarden. Het exploreren en formuleren van deze waarden helpt om zorgvuldige beslissingen te maken die passen bij de ouders en hun situatie.

Binnen de neonatologie zijn daarnaast veel ontwikkelingen, één daarvan is de artificiële placenta technologie. Deze techniek heeft als doel om extreem vroeggeboren baby's buiten de baarmoeder verder te laten ontwikkelen en daarmee lange termijn effecten te verbeteren en het overlijden van kinderen die extreem te vroeg geboren zijn te voorkomen. Deze ontwikkeling roept belangrijke vragen op.

In dit deel van mijn proefschrift worden de studies samengevat met een beknopte beschrijving van de resultaten.

De volgende doelstellingen van deze thesis zijn uiteengezet:

- Het verkennen van de waarden die belangrijk zijn in de behandelbeslissing over het starten van neonatale intensive care behandeling of palliatieve comfortzorg na een extreme vroeggeboorte op de grens van levensvatbaarheid, volgens volwassenen die zelf extreem te vroeg geboren zijn en ouders die ervaring hebben met een (dreigende) extreme vroeggeboorte;
- Het verkennen van verschillende perspectieven van diverse belanghebbenden op de ontwikkeling van de artificiële placenta technologie, met specifieke aandacht voor ethische zorgen en overwegingen rond de eerste klinische studies op mensen in de context van het beoogde doel: het bieden van behandeling voor extreem vroeggeboren kinderen.

Deze thesis is opgebouwd uit twee delen.

Deel I: waarden in de besluitvorming op de grens van levensvatbaarheid

Het **eerste deel**, bestaande uit drie hoofdstukken en twee intermezzo's, richt zich op de waarden die belangrijk zijn in de besluitvorming tussen actieve opvang en palliatieve comfortzorg op de grens van levensvatbaarheid.

Hoofdstuk 2 beschrijft de resultaten van een literatuurstudie over de waarden die voor ouders belangrijk zijn in de behandelbeslissing op de grens van levensvatbaarheid. In samenwerking met ouders van een extreem te vroeg geboren kind werd een analyse uit-

gevoerd van 17 artikelen. Deze analyse gaf inzicht in de belangrijkste waarden die voor ouders een rol spelen bij de beslissing tussen actieve opvang en palliatieve zorg. De resultaten waren complex en gelaagd. Thema's varieerden van het overwegen van feitelijke informatie over de prognose voor het kind en het gezin, tot onderliggende en soms conflicterende waarden. Andere thema's betroffen voorkeuren rond het beslissingsproces zelf, zoals de wens om "alles te proberen", of gevoelens en intuïties zoals het instinct om het kind te redden.

Intermezzo A geeft het woord aan de ouders die meewerkten aan de scoping review. Zij delen hun persoonlijke ervaringen met extreme vroeggeboorte en geven inzicht in de moeilijke keuzes die zij hebben moeten maken. Ze beschrijven welke overwegingen voor hen belangrijk waren, en hoe emoties en intuïtie een bepalende rol speelden in hun besluitvorming. Hun perspectieven dienden mede als inspiratie voor de interviewgids van de TINY-2 studie.

Hoofdstuk 3 beschrijft de resultaten van de TINY-1 studie, waarin volwassenen zijn geïnterviewd die zelf extreem te vroeg geboren zijn. Vier groepsinterviews met in totaal 23 deelnemers gaven inzicht in hun perspectieven op behandelbeslissingen rond de start van actieve opvang of palliatieve comfort zorg na een extreme vroeggeboorte. Deelnemers benadrukten het belang van het bespreken van verwachtingen en onzekerheden rondom de individuele prognose van het kind. Daarnaast wezen zij op de levenslange gevolgen van extreme vroeggeboorte, zowel voor henzelf als voor het gezin. Ook kwam naar voren dat de huidige nazorg voor deze doelgroep als ontoereikend werd ervaren met de wens voor meer gespecialiseerde klinieken en programma's die aansluiten op hun specifieke behoeften. De groep omschreef extreem prematuur geboren zijn als "een levenslange diagnose", wat de blijvende impact op hun gezondheid en welzijn benadrukte.

Als vervolg op deze bevindingen werd, in samenwerking met de deelnemers, een artikel geschreven voor *Medisch Contact* (Intermezzo B). Hierin werd aandacht gevraagd voor meer bewustwording en ondersteuning van volwassenen die extreem te vroeg geboren zijn. Het artikel bevatte voorstellen zoals gepersonaliseerde nazorg, alternatieve uitkomstmaten, meer onderzoek naar langetermijngevolgen, het opnemen van geboorteachtergrond in patiëntendossiers, en de oprichting van een nationaal expertisecentrum voor extreme vroeggeboorte.

Hoofdstuk 4 presenteert de resultaten van de TINY-2 studie, een kwalitatieve interviewstudie met ouders die een (dreigende) extreme vroeggeboorte meemaakten. In totaal werden negentien interviews afgenomen. Ouders benoemden uiteenlopende overwegingen en waarden die voor hen belangrijk waren in de beslissing tussen actieve opvang en palliatieve zorg na een extreme vroeggeboorte. Deze overwegingen draaiden vaak om de toekomst van het kind en de gevolgen voor het gezin. Ouders gaven aan dat zowel rationele als intuïtieve processen meespeelden, waarbij intuïtie en gevoel vaak de overhand hadden. Daarnaast noemden zij manieren waarop zorgprofessionals hen kunnen ondersteunen bij

het verhelderen van hun waarden, bijvoorbeeld via voorbeeldvragen tijdens counseling. Ze benadrukten ook het belang van heldere en onbevooroordeelde informatie, tijd om na te denken, en een multidisciplinaire benadering waarbij de juiste professionals betrokken zijn.

Deel II: perspectieven op de ontwikkeling van de artificiële placenta technologie

Het **tweede deel** richt zich op ethische vraagstukken en zorgen rondom de ontwikkeling van de artificiële placenta technologie. Dit deel bestaat uit vijf hoofdstukken en één intermezzo.

Hoofdstuk 5 presenteert de resultaten van een literatuurstudie naar het ethische debat over deze nieuwe artificiële placenta technologie. In totaal werden 45 artikelen geanalyseerd en onderverdeeld in drie hoofdthema's. Het eerste thema, *fundamentele ethische kwesties*, gaat over uiteenlopende opvattingen over de morele status van wat door de technologie wordt ondersteund: wordt dit gezien als een baby of als een geheel nieuwe morele categorie? Het tweede thema, *reproductieve ethiek*, behandelt de vraag of de technologie reproductieve keuzes verruimt of juist beperkt. Hierbij kwamen zorgen naar voren over maatschappelijke druk om de technologie toe te passen bij gezonde zwangerschappen of als alternatief voor abortus. Het derde thema, *onderzoeksethiek*, richt zich op de ethische uitdagingen bij het selecteren van deelnemers voor de eerste klinische studies. De review concludeert dat het ethische debat vooral gericht is op scenario's zoals het gebruik van deze technologie bij gezonde zwangerschappen of als vervang na abortus, en in mindere mate op het oorspronkelijke doel: de behandeling van kinderen die extreem te vroeg geboren zijn. Daarnaast bleek dat onderzoek onder stakeholders nog grotendeels ontbreekt, wat de noodzaak onderstreept van verdere dataverzameling en gerichte ethische analyse binnen de neonatale en perinatale zorg.

Hoofdstuk 6 beschrijft een reactie op de review van De Bie et al., getiteld *Ethics considerations regarding artificial womb technology for the fetonate*. In dit hoofdstuk wordt voorgesteld het ethische debat te verbreden met behulp van een ander normatief kader, zoals de *capability approach*. Ook wordt het gebruik van *begeleidingsethiek* aanbevolen om het maatschappelijk gesprek over artificiële placenta-technologie op een verantwoorde manier te voeren. Deze benadering kan helpen om technologische innovaties zorgvuldig te ontwikkelen en te implementeren.

Als eerste stap in de TINY-3 studie werd een workshop *Begeleidingsethiek* georganiseerd om data te verzamelen en stakeholders actief te betrekken bij de ethische beoordeling van de technologie. De resultaten van deze workshop zijn vastgelegd in een verslag (Intermezzo C). Belangrijke thema's die naar voren kwamen waren: (I) het formuleren van voorwaarden voor de eerste klinische studies op mensen, (II) zorgen over het informed consent-proces bij deze onderzoeken, (III) ethische kwesties rond implementatie, zoals ongelijkheid en onbedoelde effecten, en (IV) de rol van technologisch ontwerp in het aanpakken van deze risico's. Op basis van deze resultaten werden aanvullende focusgroepen en individuele

interviews gehouden met ouders en zorgprofessionals, om de thema's verder uit te diepen. De bevindingen hiervan worden besproken in hoofdstukken 7 tot en met 9.

Hoofdstuk 7 presenteert de resultaten van de TINY-3a studie, waarin is onderzocht hoe stakeholders aankijken tegen het ontwerp van de eerste klinische studies met de artificiële placenta technologie bij mensen. Belangrijke aandachtspunten waren: het optimaliseren van het diermodel, het helder definiëren van het primaire doel van de proef, zorgvuldige selectie van de onderzoekspopulatie, het opstellen van duidelijke stop- en succescriteria, de rol van ouders binnen de proef, en het ontwikkelen van goed onderbouwde onderzoeksprotocollen.

Hoofdstuk 8 beschrijft de resultaten van de TINY-3b studie, die zich richt op counseling en het informed consent-proces bij deelname aan deze eerste klinische studies. De studie bracht belangrijke thema's aan het licht, zoals de morele en juridische status van het wezen dat in de artificiële placenta technologie wordt ondersteund, de zwangere persoon als eerste deelnemer aan het onderzoek, en de terminologie die wordt gebruikt om de technologie te beschrijven. Ook werd de complexiteit van counseling en toestemming besproken, met speciale aandacht voor de rol van hoop bij ouders. De thema's bleken sterk met elkaar verweven: de juridische en morele context beïnvloedt de manier waarop counseling en informed consent moeten worden vormgegeven.

Hoofdstuk 9 presenteert de resultaten van de TINY-3c studie, waarin de belangrijkste ethische zorgen van stakeholders rondom de toekomstige implementatie van de technologie aan bod kwamen. De volgende zorgen werden onder andere genoemd: de mogelijke verschuiving van de grens van levensvatbaarheid, de maakbaarheid van de wereld, het afwegen van risico's tegenover mogelijke baten, en kwesties rond rechtvaardige verdeling van zorg, toegankelijkheid en gelijkheid in de zorgverlening.

List of abbreviations

AAPT	Artificial Amnion and Placenta Technology
AP	Artificial Placenta
AWT	Artificial Womb Technology
BPD	Bronchopulmonary Disease
COREQ	Consolidated Criteria For Reporting Qualitative Research
EIC	Early Intensive Care
EPI(s)	Extreme Premature Infant(s)
EVE	Ex-Vivo Uterine Environment
EXTEND	EXTra-uterine Environment for Neonatal Development
GA	Gestational Age
GEA	Guidance Ethics Approach
HCP(s)	Health Care Professional(s)
NICU	Neonatal Intensive Care Unit
NL	The Netherlands
PCC	Palliative Comfort Care
PLS	Perinatal Life Support
QoL	Quality of Life
SDM	Shared Decision Making
TINY	Toward INdiviualized care for the Youngest
UK	United Kingdom
USA	United States of America
VC	Value Clarification
WHO	World Health Organization

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Curriculum vitae

Angret de Boer werd op 5 juni 1996 geboren in Groningen. Als tweede van vier kinderen groeide ze op in Nieuw Roden, een klein dorp in het noorden van Drenthe. Na het behalen van haar gymnasium diploma op het Willem Lodewijk Gymnasium in 2014 startte zij met de opleiding Geneeskunde aan de Radboud Universiteit in Nijmegen. Tijdens haar coschappen in 2020, toen deze tijdelijk stillagen vanwege de COVID-19-pandemie, volgde zij haar wetenschappelijke stage bij de afdeling Neonatologie van het Amalia Kinderziekenhuis. Onder begeleiding van dr. Rosa Geurtzen, in samenwerking met dr. Marije Hogeveen en dr. Marieke de Vries, schreef zij een scoping review over de waarden van ouders die belangrijk waren in de besluitvorming op de grens van levensvatbaarheid. Dit zou later het tweede hoofdstuk van dit proefschrift worden. Hier begon de interesse en nieuwsgierigheid in complexe besluitvorming en de ethiek binnen de neonatologie. Vlak voor haar afstuderen werd zij voorgesteld aan dr. Joanne Verweij, die op dat moment samen met Lien De Proost onderzoek deed naar de richtlijn perinataal beleid bij extreme vroeggeboorte en personalisatie van zorg op de grens van levensvatbaarheid. Dit markeerde het begin van een waardevolle samenwerking. Na haar afstuderen in oktober 2019 begon Angret direct als arts-onderzoeker op de afdeling Verloskunde en Gynaecologie van het Leids Universitair Medisch Centrum. Uiteindelijk resulteerde dit in een promotietraject onder begeleiding van prof. dr. Martine de Vries (ethiek en recht), dr. Joanne Verweij (verloskunde) en dr. Rosa Geurtzen (neonatologie). Gedurende haar promotietraject heeft Angret diverse cursussen gevolgd ter verbreding en verdieping van haar academische vorming, waaronder de OZSW-cursus *Biomedical Ethics* en behaalde zij haar BROK-certificaat (*Basiscursus Regelgeving en Organisatie voor Klinisch Onderzoekers*). Daarnaast nam zij onder andere deel aan een workshop van de Brocher Foundation over de artificiële placenta technologie en presenteerde zij haar onderzoek op nationale en internationale congressen.

Sinds februari 2025 is Angret werkzaam als ANIOS kindergeneeskunde in het Rijnstate ziekenhuis Arnhem.

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