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

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Chapter 10

English summary and general discussion

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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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