Interprofessional Consensus Regarding Design Requirements for Liquid-Based Perinatal Life Support (PLS) Technology

Citation for published version (APA):
vander Hout-van der Jagt, M. B., Verweij, E. J. T., Andriessen, P., de Boode, W. P., Bos, A. F., Delbressine, F. L. M., Eggink, A. J., Erwich, J. J. H. M., Feijs, L. M. G., Groenendaal, F., Kramer, B. W. W., Lely, A. T., Loop, R. F. A. M., Neukamp, F., Onland, W., Oudijk, M. A., te Pas, A. B., Reiss, I. K. M., Schoberer, M., ... Oei, S. G. (2022). Interprofessional Consensus Regarding Design Requirements for Liquid-Based Perinatal Life Support (PLS) Technology. Frontiers in Pediatrics, 9, [793531]. https://doi.org/10.3389/fped.2021.793531

DOI:
10.3389/fped.2021.793531

Document status and date:
Published: 19/01/2022

Document Version:
Publisher’s PDF, also known as Version of Record (includes final page, issue and volume numbers)

Please check the document version of this publication:
• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher’s website.
• The final author version and the galley proof are versions of the publication after peer review.
• The final published version features the final layout of the paper including the volume, issue and page numbers.

Link to publication

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license above, please follow below link for the End User Agreement:
www.tue.nl/taverne

Take down policy
If you believe that this document breaches copyright please contact us at:
openaccess@tue.nl
providing details and we will investigate your claim.

Download date: 09. Jun. 2022
Interprofessional Consensus Regarding Design Requirements for Liquid-Based Perinatal Life Support (PLS) Technology

M. Beatrijs van der Hout-van der Jagt, E. J. T. Verweij, Peter Andriessen, Willem P. de Boode, Arend F. Bos, Frank L. M. Delbressine, Alex J. Eggink, Jan Jaap H. M. Erwich, Loe M. G. Feijs, Floris Groenendaal, Boris W. W. Kramer, A. Titia Lely, Rachel F. A. M. Loop, Franziska Neukamp, Wes Onland, Martijn A. Oudijk, Arjan B. te Pas, Irwin K. M. Reiss, Mark Schoberer, Ralph R. Scholten, Marc E. A. Spaanderman, Myrthe van der Ven, Marijn J. Vermeulen, Frans N. van de Vosse and S. Guid Oei

Open Access

Edited by: Claus Klingenberg, Arctic University of Norway, Norway
Reviewed by: Janice Sylver, Norwegian University of Science and Technology, Norway
Elisabeth Olhager, Lund University, Sweden

Correspondence: M. Beatrijs van der Hout-van der Jagt m.b.v.d.hout@tue.nl

This article was submitted to Neonatology, a section of the journal Frontiers in Pediatrics

Received: 12 October 2021
Accepted: 14 December 2021
Published: 19 January 2022

Citation: van der Hout-van der Jagt MB, Verweij EJT, Andriessen P, de Boode WP, Bos AF, Delbressine FLM, Eggink AJ, Erwich JHM, Feijs LMG, Groenendaal F, Kramer BW, Lely AT, Loop PFAM, Neukamp F, Onland W, Oudijk MA, te Pas AB, Reiss IKM, Schoberer M, Scholten RR, Spaanderman MEA, van der Ven M, Vermeulen MJ, van de Vosse FN and Oei SG (2022) Interprofessional Consensus Regarding Design Requirements for Liquid-Based Perinatal Life Support (PLS) Technology. Front. Pediatr. 9:793531. doi: 10.3389/fped.2021.793531

Liquid-based perinatal life support (PLS) technology will probably be applied in a first-in-human study within the next decade. Research and development of PLS technology should not only address technical issues, but also consider socio-ethical and legal aspects, its application area, and the corresponding design implications. This paper represents the consensus opinion of a group of healthcare professionals, designers, ethicists, researchers and patient representatives, who have expertise in tertiary obstetric and neonatal care, bio-ethics, experimental perinatal animal models for physiologic research, biomedical modeling, monitoring, and design. The aim of this paper is...
to provide a framework for research and development of PLS technology. These requirements are considering the possible respective user perspectives, with the aim to co-create a PLS system that facilitates physiological growth and development for extremely preterm born infants.

Keywords: perinatal life support, artificial placenta, AAPT, user perspectives, design implications, value-sensitive design

INTRODUCTION

Preterm birth is the leading cause of perinatal and neonatal mortality and life-long morbidity world-wide (1). After birth, especially extremely preterm born infants (<28 weeks of gestation) face a challenging transition from fetal to neonatal physiology due to organ immaturity (2). The transition is often complicated by a variety of (sudden) incidents, including heat loss from an immature skin, the necessity of respiratory support, disrupted circulatory adaptations, nutrition deficiency and infections due to an immature immune system and invasive procedures (3, 4). Current treatment requires preterm initiation of body functions for which the respective organs are not yet prepared. This affects primarily the lungs, responsible for gas-exchange (often dependent on mechanical ventilation); the heart, responsible for tissue perfusion and oxygenation; the gut, needed for energy and nutrition; and the brain, with high vulnerability for cerebral hemorrhage (3–5). Consequently, despite the clinical advances at neonatal intensive care units (NICU), still too many extremely preterm but viable infants will suffer permanent health complications.

For decades, researchers have been looking for liquid-based incubators to mimic intra-uterine life for premature new-born infants to prolong fetal physiology (6, 7). Also, the concept of ectogenesis has been described by numerous authors in the beginning of the 20th century (8), and a first patent was filed in 1955 (9).

Based on current scientific advances, it is likely that, following thorough clinical research, PLS technology will ultimately be introduced into clinical practice (10), as an alternative treatment option to conventional neonatal care (11). Research groups in both the US, and in Australia and Japan, recently presented promising pre-clinical results for (extreme) preterm born lambs (12–14). As PLS technology is still developing, a vision on both co-creation of PLS technology and on clinical application of PLS is required, as this will determine design requirements, and also societal acceptance. Therefore, a value-sensitive design approach is preferred (15, 16).

On the one hand, PLS technology yields exciting health promises for mothers and fetuses at risk, as fetal and maternal treatment might now be individually optimized, rather than facing trade-offs between optimizing imperfectly aligned maternal and fetal outcomes (17). Indeed, when successful, i.e., when PLS-based treatment would allow human fetal development and organ maturation as in utero, (life-long) complications following preterm birth and neonatal (intensive) care could be prevented (12–14). On the other hand, the technology raises important societal-ethical and legal issues (17–21). Recently, we have established a consortium of healthcare professionals, designers, ethicists, researchers and patient representatives to contribute to the development of PLS technology. In this paper, we present the consensus opinion of this consortium, and propose our vision on the design requirements of PLS-based development. This will provide a framework in which we think this research should be carried-out, based on our vision that PLS-based treatment should be an evolutionary extension of future treatment options in neonatal critical care, for a patient group that presently is already considered eligible for neonatal treatment. Moreover, prior to any form of clinical testing with humans, all potential technical hurdles have to be addressed within this framework. It is of the utmost importance that any development in this field is actively accompanied by socio-ethical debate, rather than that a fully developed technology is being introduced without ongoing debate. To this end, a roadmap on the ethical development of PLS technology has been recently presented by Verweij et al. (16).

KEY ELEMENTS

PLS

PLS refers to application of perinatal life support systems for “developing fetuses” outside the womb, prior to the physiological transition from fetal to neonatal physiology as induced by birth (17, 22). This transition is marked by a cascade of physiological events that among other result in the initiation of breathing and the re-routing of blood flows to accommodate lung circulation as permanent replacement of umbilical and placental circulation (23). To utilize PLS, the initiation of this physiological cascade has to be prevented when the infant leaves the intra-uterine environment, in order to allow further growth and maturation using an artificial placenta (12–14). PLS thus takes over maternal and placental physiological functions, i.e., a form of artificial amnion and placenta technology, also referred to as AAPT (22). By definition, application of PLS implies that the infant has fluid-filled lungs, and/or that the infant is immersed in liquid. It also implies that oxygenation is secured through external oxygen delivery to the infant’s blood, thereby bypassing its lungs.

PLS Transfer Procedure

The transfer of the fetus from the womb to the PLS system has to take place without inducing the physiological cascade of fetal to neonatal transition. It therefore requires fast vascular access through the umbilical vessels to enable connection of the infant’s circulation to the artificial placenta (12, 13, 24). Reported animal studies therefore performed a cesarean section, as labor and spontaneous birth set off the cascade of processes in preparation.
of extra-uterine life (12, 13). For a successful transfer to the PLS system, the transition to neonatal physiology has to be prevented through a safe childbirth procedure for both mother and fetus. Hence, PLS-based treatment after vaginal birth will remain a possibility if fetal breathing and umbilical vascular spasm can be prevented, contamination can be contained and/or fetal infection can be treated (24).

The Perinate
The infant subject to PLS clearly cannot be categorized based on either the characteristics of a fetus or a neonate: it has been “born-by location change,” but not yet “born-by-physiology-change” (22). The term “gestating” has been introduced as a definition for an individual with fetal physiology being gestated outside the human body (17), and this has been adopted by others (22). However, this term also refers to (as yet completely hypothetical) cases of both complete ectogenesis and ectogenesis before the threshold of viability. Therefore, we introduce perinate as a subcategory of the gestating, as this term reflects the perinatal stage the infant is in: “peri” (around) “natus” (birth, born), and thus to mark the temporary and specific purpose of perinatal incubation after (extreme) preterm birth as an alternative to perinatal and neonatal care. During a second transition, the perinate is weaned from the perinatal life support and thus becomes a neonate. This involves a complete transition from fetal to neonatal physiology, comparable to normal birth.

VISION

PLS Technology Requirements
PLS-based treatment should not be considered as replacement therapy for pregnancy (22), but as an alternative to state-of-the-art neonatal care (17). We envision a PLS environment inspired by, and mimicking the natural womb as much as possible to provide an environment for the perinate that meets all physiological requirements related to the not yet “born-by-physiological-change” principle (22). This implies that design requirements will as much as possible align with the natural environment. Therefore, we propose a perinate-centric perspective that also values the criteria from the other user groups: mother, family and healthcare professionals.

Perinate’s Perspective
From the perspective of the perinate, PLS should be unobtrusive and non- or minimal invasive, and should provide a similar sensation as intra-uterine life. Ideally, the perinate should not be able to differentiate between the intra-uterine and the PLS environment, such that optimal physical, psychosocial and mental health development is enabled and stimulated. To meet this criterion, a set of goals can be defined:

- Fetal physiology needs to be preserved. Hence, the umbilical cord should be the single access point to the fetus, and the placental function has to be mimicked.
- The perinate should receive equal sensory input as during intra-uterine life. This includes stimuli originating from both inside and outside the maternal body, by providing interaction with the surrounding: e.g., auditory and motion stimuli to “experience” the presence of the mother and other family members, either (in)direct or through simulation.
- The perinate should show normal growth and development, expressed not only as physical growth, but also as normal biomarker values (e.g., blood composition), autonomous nervous system development and fetal behavior to facilitate normal psycho-social development.

These goals align with current views presented in literature, displaying that the physiologic needs of the subject of PLS-based treatment are equal to the physiologic needs of an unborn fetus (17–22, 25–27).

Maternal Perspective
PLS will have a complex and major impact on the mother, that goes beyond the experience of giving extreme preterm birth. She might experience a discrepancy as she is not pregnant anymore, while her child is not yet born but being incubated using PLS. As PLS by definition takes over her physiologic function during gestation, special attention is needed for her physical and psychological needs during both the transfer to the PLS system and the perinate’s stay in the PLS system, to minimize maternal stress and facilitate bonding (28). Also, a woman cannot be forced to undergo a cesarean section, even if this will save the life of the unborn child (19, 29, 30). This yields the following criteria:

- The use of PLS should not be restricted to clinical procedures based on cesarean section, but also be compatible with vaginal birth.
- The mother should be enabled to transfer normal, pregnancy-related stimuli to the perinate, such as maternal movements, sounds, endocrine stimuli, and vocal stimuli.
- The mother should be fully supported in her physiological needs and needs to be supported with the after-effects of delivery, such as the onset of lactation and recovery.
- Maternal psychological aspects need to be addressed, including a positive attitude that despite a medical necessity for using PLS, the infant can develop as much as possible in a physiological manner. In addition, attention has to be paid to avoid her having a feeling of guilt toward her baby for not continuously being present during this important developmental stage. We envision to differentiate carefully between functions of the placenta and role of the mother. The latter is much more complex and needs to be supported in all aspects.

Although PLS-based therapy is not considered as a replacement for pregnancy, it can be considered to provide the mother with an option to experience the presence of the perinate, albeit simulated, by using technology e.g., to sense movements of the perinate.

Family Perspective - Family-Centered Care
The other parent and siblings of the perinate are also affected by the use of PLS, especially with respect to the important process of bonding and the psychological impact. Hence, PLS technology should facilitate and stimulate bonding by allowing other family members to interact with the perinate, whereas
psychological aspects need to be addressed during the care process. Hence, PLS-based treatment should allow and encourage active parental involvement, even though direct interaction might be challenging regarding its potential interference with normal growth and development and risk for infection. When considering (discontinuation of) PLS treatment, this should be accompanied with timely and respectful counseling and shared-decision-making to prevent moral pressure and therapeutic misconception (31).

Healthcare Professional Perspective
PLS technology should facilitate healthcare professionals in caring for the perinate. Hence, the following sub-goals can be defined:

- PLS technology should provide healthcare professionals with information: clear, correct and timely data, where signals are converted into meaningful and interpretable information, using a clinical decision support system based on digital twins of both the perinate and the PLS system, and provide early warning (32).
- PLS technology should provide suitable access points for clinical care, in a least complex and safe manner, to prevent medical and patient safety errors.
- Healthcare professionals need to be able to interfere and override PLS technology in case of emergency. The final responsibility rests with the clinician in charge, not the system.
- The care team should include people with knowledge on clinical care, physiology, technical care, growth and development, perinatology and neonatology. The team should have one medical, and one technical responsible leader, with joint final responsibility.

PLS TECHNOLOGY AS NEW APPROACH TO PERINATAL CARE

Design Implications
The different user perspectives all underline that PLS technology should mimic and emphasize the natural functions of the physiological womb. The following design implications have been derived by stakeholder input, i.e., of healthcare professionals, designers, ethicists, researchers and patient representatives, based on this integral vision. The design implications should drive technological feasibility, not the other way around. Indeed, innovations follow clinical and technical challenges.

Placenta
Due to its vascular architecture, the placenta cannot be detached from the uterus for use in an extrauterine environment but has to be replaced by an artificial organ. The most vital placental function is gas exchange. Therefore, oxygenators, connected to the circulation via the umbilical vessels in experimental research, have been used and referred to as artificial placenta since the late 1950s (6, 7). Technological advance has led to a reduction of size and resistance, thereby allowing to use pumpless extracorporeal circuits (12, 14, 33, 34). Other important placental functions include metabolic waste products removal, hormones formation, supply of micro- and macronutrients, and the transfer and accumulation of (maternal) antibodies into the fetal blood (35). Of these, the elimination of urinary excreted substances would be most likely technical feasible with current medical technology (36). Technical challenges lie within the objective to minimize activation of coagulation and inflammation induced by foreign surfaces (37), and in appropriate sizing.

External Stimuli
In utero, sensory stimuli are essential for physiologic development of the senses (38). PLS technology should offer natural sensory input to the perinate as to stimulate normal growth and (neurological) development. Sensory stimuli, both originating from the maternal biological environment as from the outside world, should be applied to the perinate using targeted technology. Individualized inputs can be either simulated, pre-recorded or real-time, and can include maternal physiological sounds (like heartbeats), maternal movements, uterine contractions, diurnal rhythm, maternal endocrine factors, etcetera.

Chamber-Within-Chamber Design
We envision a closed system that stretches with the perinate's growth, such that the perinate has little perception of the differences between the real and mimicked womb. As every fetus has its unique intra-uterine environment, a chamber-within-chamber design for the PLS system should be provided. The inner chamber provides a liquid-based environment with sterile artificial amniotic fluid, while the outer chamber can be used to apply auditory, visual and tactile stimuli in a controlled environment specific for each perinate.

Medical Treatment
PLS technology should allow medical treatment and administration of drugs, appropriate for the perinate's needs. Administration and access routes can be multiple: artificial placenta, amniotic fluid, etcetera. For manual access to the perinate, e.g., for emergency delivery or fetal therapeutic treatment such as surgery, the inner chamber should be accessible, and a procedure to prevent any infection provoked by opening the chamber should be in place.

Monitoring
Continuous and tailored monitoring of the perinate's growth and well-being contributes both to fine-tuning of the system's life support functions and in decision-making. Monitoring includes electrocardiography, electroencephalography, movements, nutritional status, oxygenation, carbon dioxide exchange, fluid balance, temperature, biomarker and metabolite concentrations, blood count, circulatory and kidney function, using sensor technology and metabolomics analysis. The collected data will provide insights into perinatal physiological and pathophysiological processes, circadian rhythms and the influence of environmental factors like nutrition, light and physical stimuli on perinatal wellbeing.
Clinical Transfer Procedures
First transfer: Sterile and smooth birth by cesarean section or vaginal delivery, whereby the perinate is protected against breathing while being transferred from the uterus into an airtight bag. This procedure should be as least interfering with the perinate’s perception as possible, as the perinate should experience the PLS system as if no birth has taken place. Also, this procedure should promote best maternal physical and psychological health. Second transfer: Simulated birth when the perinate leaves the PLS system: this transfer finalizes birth and should represent the beneficial effects of an actual birth as much as possible. This could include applying uterine contractions to the PLS system and providing a passage of the infant through a simulated birth canal.

PLS Technology Research and Development
Research and development of PLS technology should be driven by the design requirements and is obviously influenced by current technological advances and limitations. Indeed, PLS-based research faces many research challenges, e.g., regarding the abandonment of systemic anticoagulation, the need for a much deeper knowledge of the molecular functions of the feto-placenta-maternal unit, and the inflammatory effects of technical devices. Yet, technological innovation can only follow from a clear vision and related design requirements. While developing working prototypes, thorough testing in a simulated environment with computer models and high-fidelity physical manikins is highly recommended. After such technical validation, animal experiments in established animal models (12, 14, 39–43) can confirm the feasibility to promote a clinical trial.

Implications for Clinical Care
Clinical care using PLS technology should be carried out on a specific perinatal intensive care unit, in which obstetric high care and neonatal intensive care are integrated in a family-centric approach. PLS-based treatment should be trusted to a specifically trained care team, consisting of medical and technical professionals that work in respectful dialogue with the parents. This may lead to new clinical specialisms, such as a “perineonatologist” with knowledge of maternal, fetal and perinatal physiology; technical specialists; perfusionists; specialized anesthesiologists; specialized nurses; social workers and psychologists. Obviously, research should include thorough in vitro and in silico testing, animal experiments, and (pre-)clinical trials. Moreover, in-depth evaluation of both short- and long-term clinical outcome of infants treated with PLS-based procedures has to provide evidence on whether PLS-based treatment is superior to current treatment options, before it is widely implemented (11).

DISCUSSION
PLS-based treatment is an exciting and promising method to limit or even prevent the consequences of extreme preterm birth. When designing PLS technology, the natural womb should as much as possible set the design requirements; and current advances in technology are encouraging. Application of PLS comes with ethical and societal responsibilities, as has been elaborated in a recently presented roadmap on the ethical development of PLS technology (16). Hence, even if all technical challenges would be met, ethical, legal and societal implications should be considered carefully, as the availability of PLS will highly influence societal values and perceptions regarding e.g., pregnancy, childbirth, women and (unborn) babies, but also the moral and legal status of the perinate. Therefore, we advocate stakeholder involvement and a value-sensitive design approach throughout the research and development process (16).

Human research ethics for PLS needs further study to address important aspects like patient selection and informed consent (16). Similarly to selecting appropriate patient groups for clinical trials (11), also once clinically implemented this mandates a head-to-head comparison with standard neonatal care. One of the most important aspects will be the counseling strategy (16). PLS could be an answer to the dilemma of the benefits outweighing the risks of continuing pregnancy vs. the health risks involved for either the mother or the infant (17). Yet, first has to be investigated whether PLS-based treatment is superior to the current standard of treatment (11, 44). Without evident proof on the short- and long-term implications of infants being gestated using PLS, great caution is needed. In addition, we strongly urge teams involved in the development of PLS-based treatment to embrace and build on all valuable things learned in conventional antenatal and neonatal care. These include essential concepts as shared decision-making, counseling at the border of viability, family-centered care and the NIDCAP approach to neonatal development (45). Ultimately, knowledge acquired in PLS-based research and clinical care should help to improve standard care as well.

DATA AVAILABILITY STATEMENT
The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS
MH wrote the main manuscript text based on a discussion session with FD, LF, RL, MO, RS, FV, and SO and separate consultation with IR, EV, and MV. All authors provided further input and reviewed the manuscript.

FUNDING
This work was funded in part by the European Union via the Horizon 2020: Future Emerging Topics call (FET Open), Grant EU863087, project PLS.

ACKNOWLEDGMENTS
The manuscript was drafted on behalf of two consortia. All consortium members have been informed on the publication and could provide feedback on the final draft. PLS Consortium of Project “Perinatal Life Support System: Integration of
Enabling Technologies for Clinical Translation” Under Horizon 2020 FET Open Grant EU863087 With Project Partners Eindhoven University of Technology, Eindhoven, Netherlands; Universitätsklinikum Aachen, Aachen, Germany; LifeTec Group, Eindhoven, Netherlands; Politecnico di Milano, Milan, Italy; Nemo Healthcare BV, Eindhoven, Netherlands. Dutch Consortium “Toward an Artificial Womb for Extremely Premature Born Infants”, With Partners Eindhoven University of Technology, Eindhoven, Netherlands; Erasmus MC, Rotterdam, Netherlands; Amsterdam UMC, Amsterdam, Netherlands; Radboud UMC, Nijmegen, Netherlands; UMC Groningen, Groningen, Netherlands; LUMC, Leiden, Netherlands; Maastricht UMC+, Maastricht, Netherlands; UMC Utrecht, Utrecht, Netherlands; University of Twente, Enschede, Netherlands; Delft University of Technology, Delft, Netherlands

PLS Consortium “Perinatal Life Support” consists of the following members:

F. L. M. Delbressine1, L. M. G. Feijs1, J. S. van Haren1,2, M. B. van der Hout-van der Jagt2,3,4, S. G. Oei2,4, M. C. M. Rutten4, M. W. H. Thielens1, M. van der Ven2,4, F. N. van de Vosse1, B. G. van Willigen2,3, S. Jansen5, F. Neukamp6, M. Schoberer7, U. Steinseifer7, D. Contini8, A. Torricelli8, M. D’Alessi8, M. Stijnen9,10, R. Kok8, C. Peters8, R. Vullings4,8

Dutch Consortium “Dutch Universities” consists of the following members:

H. K. G. Andersen1, P. Andriessen9,10, R. N. A. Bekkers11, J. W. M. Bergmans4, F. L. M. Delbressine1, L. M. G. Feijs1, L. E. Frank11, M. B. van der Hout-van der Jagt2,3,4, E. M. Kingma11, D. Kommers9,10, J. O. E. H. van Laar2,4, R. F. A. M. Loop1, M. Mischi4, H. J. Niemarkt9,10, S. G. Oei2,4, M. C. M. Rutten4, M. W. H. Thielens1, M. van der Ven2,4, F. N. van de Vosse1, D. R. R. van der Woude2,4, A. H. L. C. van Kaami12, W. Onland12, M. A. Oudijk13, C. Ris-Stalpers14, L. van Stekelenburg15, C. J. M. Verhoeven16, M. Zuiderveld17, J. Dankelman18, P. P. van den Berg19, A. F. Bos20, J. J. H. M. Erwich19, A. B. te Pa21, F. Slaghekke9,22, E. J. T. Verweij9,22, H. ten Cate23, B. W. W. Kramer24, M. E. A. Spaanderman25,26, H. M. H. Spronk23, W. P. de Boode27, J. van Drongelen27, A. F. J. van Heijst27, R. R. Scholten27, A. J. Eggink28, H. Ismaili M’Hamdi29, E. J. Oldekerk30, I. K. M. Reiss31, M. J. Vermeulen31,32, J. Arens33, M. N. Bekker34, M. J. N. L. Benders35, K. W. M. Bloemenkamp34, J. B. Derks34, F. Groenendaal35, A. T. Lely34, C. H. A. Nijboer35, J. van Eyck36

1Department of Industrial Design Engineering, Eindhoven University of Technology, Eindhoven, Netherlands
2Department of Obstetrics and Gynecology, Maxima Medical Centre, Veldhoven, Netherlands
3Department of Biomedical Engineering, Eindhoven University of Technology, Eindhoven, Netherlands
4Department of Electrical Engineering, Eindhoven University of Technology, Eindhoven, Netherlands
5Institute for Applied Medical Engineering (AME) and Clinic for Neonatology, University Hospital Aachen, Aachen, Germany
6Politecnico di Milano, Dipartimento di Fisica, Milano, Italy
7LifeTec Group B. V., Eindhoven, Netherlands
8Nemo Healthcare, B. V., Veldhoven, Netherlands
9Department of Neonatology, Maxima Medical Centre, Veldhoven, Netherlands
10Department of Medical Physics and Engineering, Eindhoven University of Technology, Eindhoven, Netherlands
11Department of Industrial Engineering and Innovation Sciences, Eindhoven University of Technology, Eindhoven, Netherlands
12Department of Neonatology, Amsterdam UMC, Amsterdam, Netherlands
13Department of Obstetrics, Amsterdam UMC, University of Amsterdam, Amsterdam Reproduction and Development Research Institute Amsterdam, Amsterdam, Netherlands
14Department of Gynecology and Obstetrics, Academic Reproduction and Development, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands
15Faculty of Behavioral and Movement Sciences, Educational Studies, University of Amsterdam, Amsterdam, Netherlands
16Department of Midwifery Science, Amsterdam UMC, University of Amsterdam, Amsterdam Reproduction and Development Research Institute Amsterdam, Amsterdam, Netherlands
17Department of Neonatology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands
18Department of Obstetrics and Gynecology, University Medical Center Groningen, University of Groningen, Beatrix Children’s Hospital, Groningen, Netherlands
19Department of Neonatology, LUMC, Leiden, Netherlands
20Department of Obstetrics and Gynecology, Division of Fetal Therapy, LUMC, Leiden, Netherlands
21Department of Health, Medicine and Life Sciences, Maastricht University, Maastricht, Netherlands
22Department of Neonatology, Maastricht, Netherlands
23Division of Neonatology, Department of Obstetrics and Gynecology, MUMC, Maastricht, Netherlands
24Division of Obstetrics and Gynecology, Medical Centre Rotterdam, Rotterdam, Netherlands
25Department of Obstetrics, Gynecology and MUMC, Maastricht, Netherlands
26Division of Neonatology, Department of Perinatology, Radboud University Medical Center, Radboud Institute for Health Sciences, Amalia Children’s Hospital, Nijmegen, Netherlands
27Department of Obstetrics and Gynecology, Radboud Medical Centre, Nijmegen, Netherlands
28Department of Obstetrics & Gynecology, Erasmus Medical Centre, Rotterdam, Netherlands
29Department of Medical Ethics, Philosophy and History of Medicine, Erasmus Medical Centre, Rotterdam, Netherlands
30Department of Health Law, LUMC, Leiden, Netherlands
31Department of Neonatology, Erasmus Medical Centre, Rotterdam, Netherlands
32Care4Neo Foundation, Rotterdam, Netherlands
REFERENCES

1. Strong KL, Pedersen J, Johansson EW, Cao B, Diaz T, Guthold R, et al. Patterns and trends in causes of child and adolescent mortality 2000-2016: setting the scene for child health redesign. BMJ Glob Health. (2021) 6:e7460. doi: 10.1136/bmjgh-2020-004760

2. March of Dimes, PMINCH, Save the children, WHO. Born Too Soon: The Global action report on preterm birth. Eds Geneva: World Health Organization (2012). Available Online at: http://apps.who.int/bitstream/handle/10665/44864/9789241503433_eng.pdf;jsessionid=E50D2E3A9C8696531B7E29B1D9650345?sequence=1

3. Armentrout D. Not Ready for Prime Time. J Perinat Neonatal Nurs. (2014) 28:144–9. doi: 10.1097/JPN.0000000000000025

4. Evans K. Cardiovascular transition of the extremely premature infant and challenges to maintain hemodynamic stability. J Perinat Neonatal Nurs. (2016) 30:68–72. doi: 10.1097/JPN.0000000000000156

5. Bolisetty S, Dhawan A, Abdel-Latif M, Bajuk B, Stack J, Lui K. Intraventricular hemorrhage and neurodevelopmental outcomes in extreme preterm infants. Pediatrics. (2014) 133:55–62. doi: 10.1542/peds.2013-0372

6. Davis RP, Benjamin B, Mychaliska GB. A paradigm shift in the treatment of extreme prematurity: the artificial placenta. Curr Opin Pediatr. (2014) 2:370. doi: 10.1097/MOP.0000000000000083

7. Schoberer M, Arens J, Lohr A, Seehase M, Jellema RK, Collins JJ, et al. Fifty Years of Work on the Artificial Placenta: Milestones in the History of Extracorporeal Support of the Premature Newborn. Artif Organs. (2012) 36:512–6. doi: 10.1111/j.1525-1594.2011.01404.x

8. Ferreira A. The fantasy of ectogenesis in interwar Britain: texts and contexts. In: Lemos M, Gomes MR, editors. Exchanges Between Literature and Science From the 1800s to the 2000s: Converging Realms: Exchanges Between Literature and Science-from-the-1800s-to-the-2000s-converging-realms/ocd/962017196 (accessed August 4, 2021).

9. Greenberg EM. Artificial Uterus. New York, NY (1954). Available online at: https://patents.google.com/patent/US2723660A/en (accessed August 4, 2021).

10. De Bie FR, Davey MG, Larson AC, Deprest J, Flake AW. Artificial placenta and womb technology: past, present, and future challenges towards clinical translation. Prenat Diagn. (2021) 41:145–58. doi: 10.1002/pd.5821

11. Romanis EC. Artificial womb technology and clinical translation: innovative treatment or medical research? Bioethics. (2020) 34:392–402. doi: 10.1111/bioe.12701

12. Partridge EA, Davey MG, Hornick MA, McGovern PE, Mejaddam AY, Vrecenak JD, et al. An extra-uterine system to physiologically support the extremely premature lamb. Nat Commun. (2017) 8:15112. doi: 10.1038/ncomms15794

13. Usuda H, Watanabe S, Miura Y, Saito M, Musk GC, Rittenschober-Böhm J, et al. Successful maintenance of key physiological parameters in preterm lambs treated with ex utero uterine environment therapy for a period of 1 week. Am J Obstet Gynecol. (2017) 217:457.e1–457.e13. doi: 10.1016/j.ajog.2017.05.046

14. Usuda H, Watanabe S, Saito M, Sato M, Musk GC, Fee ME, et al. Successful use of an artificial placenta to support extremely preterm ovine fetuses at the border of viability. Am J Obstet Gynecol. (2019) 221:69.e1–69.e17. doi: 10.1016/j.ajog.2019.03.001

15. Friedman B, Kahn P, Borning A. Value Sensitive Design: Theory and Methods. Seattle, Univ Washington Tech (2002).

16. Verweij EJT, De Proost L, van Laar JOEH, Frank L, Oberman S, Vermeulen M, et al. Ethical development of artificial amniotic sac and placenta technology: a roadmap. Front Pediatr. (2021). doi: 10.3389/fped.2021.793308

17. Romanis EC. Artificial womb technology and the frontiers of human reproduction: conceptual differences and potential implications. J Med Ethics. (2018) 44:751–5. doi: 10.1136/medethics-2018-104910

18. Reiber DT. The Morality of Artificial Womb Technology. Natl Cathol Bioeth Q. (2010) 5:1015–27. doi: 10.5840/ncbq201010332

19. Alghrani A. In Vitro Gestation II. In: Regulating Assisted Reproductive Technologies. (2018). p. 144–78.

20. Romanis EC. Challenging the “Born Alive” threshold: fetal surgery, artificial wombs, and the english approach to legal personhood. Med Law Rev. (2020) 28:93–123. doi: 10.1093/medlaw/fzw014

21. Dodger D, Colgrove N, Blackshaw BP. Gestationicide: killing the subject of the artificial womb. J Med Ethics. (2020) 47. doi: 10.1136/medethics-2020-106708

22. Kingma E, Finn S. Neonatal incubator or artificial womb? Distinguishing ectogestation and ectogenesis using the metaphysics of pregnancy. Bioethics. (2020) 34:354–63. doi: 10.1111/bioe.12717

23. Morton SU, Brodsky D. Fetal Physiology and the Transition to Extrauterine Life. Clinics in Perinatology. (2016) 43. doi: 10.1016/clp.2016.04.001

24. Marwan A, Crombleholme TM. The EXIT procedure: principles, pitfalls, and progress. Semin Pediatr Surg. (2006) 15:107–15. doi: 10.1053/j.speu.2006.02.008

25. Horn C. Ectogenesis at Home? Artificial Wombs and Access to Care. https://Blogs.BMJ.com (2020). Available online at: https://blogs.bmj.com/medical-humanities/2020/03/03/ectogenesis-at-home-artificial-wombs-and-access-to-care/ (accessed March 30, 2021).

26. Romanis EC. Artificial womb technology and the significance of birth: why gestaltelings are not newborns (or fetuses). Journal of Medical Ethics. (2019) 45:727–9. doi: 10.1136/medethics-2019-105723

27. Romanis EC. Artificial womb technology and the choice to gestate ex utero: is partial ectogenesis the business of the criminal law? Med Law Rev. (2020) 28:342–74. doi: 10.1093/medlaw/fwz037

28. Roque ATE, Lasiuk GC, Radunz V, Hegadoren K. Scoping review of the mental health of parents of infants in the NICU. JOGNN-J Obstet Gynecol Neonatal Nurs. (2016) 45:576–87. doi: 10.1016/j.jogn.2017.02.005

29. Behrman RE, Butler AS. Preterm birth: Causes, Consequences, and prevention. In: Behrman RE, Butle AS, Healthy I of M (US) C on UPB and A, editors. Preterm Birth Causes, Consequences, and Prevention. Washington (DC): National Academies Press (US) (2007). p. 1–772.

30. Ringma E, Porter L. Parental obligation and compelled cesarean section: careful analogies and reliable reasoning about individual cases. J Med Ethics. (2020) 47:280–6. doi: 10.1136/medethics-2020-106672

31. Verweij EJT (Joanne). Ethics of involving pregnant women in fetal therapy trials. In: Schmitt-D, Clarke A, Dondorp W, editors. The Fetas as a Patient. 1st ed. Routledge (2018), p. 133–43. Available from: https://www.taylorfrancis.com/chapters/edit/10.4324/9781315170749-11/ethics-involving-pregnant-women-fetal-therapy-trials-joanne-verweij (accessed August 4, 2021).

32. Safavi KC, Driscoll W, Wiener-Kronish JP. Remote surveillance technologies: realizing the aim of right patient, right data, right time. Anesth Analg. (2019) 129:726–34. doi: 10.1213/ANE.0000000000003948

33. Arens J, Schoberer M, Lohr A, Orlikowsky T, Seehase M, Jellema RK, et al. NeonatoX: a pummless extracorporeal lung support for premature neonates. Artif Organs. (2011) 35:997–1001. doi: 10.1111/j.1525-1594.2011.01324.x

34. Schoberer M, Arens J, Erben A, Ophelders D, Jellema RK, Kramer BW, et al. Miniaturization: the clue to clinical application of the artificial placenta. Artif Organs. (2014) 38:208–14. doi: 10.1111/aor.12146

35. Department of Neonatology, Utrecht University Medical Center, Utrecht, Netherlands

36. Department of Obstetrics and Gynecology, Isala Kliniek, Zwolle, Netherlands
in critically ill patients: a systematic review. *Crit Care*. (2014) 18. doi: 10.1186/s13054-014-0675-x
37. Raffaeli G, Ghirardello S, Passera S, Mosca F, Cavallaro G. Oxidative stress and neonatal respiratory extracorporeal membrane oxygenation. *Front Physiol*. (2018) 9:1–20. doi: 10.3389/fphys.2018.01739
38. Clark-Gambelunghe MB, Clark DA. Sensory Development. *Pediatr Clin North Am*. (2015) 62:367–84. doi: 10.1016/j.pcl.2014.11.003
39. Jellema RK, Wolfs TGAM, Lima Passos V, Zwanenburg A, Ophelders DRMG, Kuypers E, et al. Mesenchymal stem cells induce T-cell tolerance and protect the preterm brain after global hypoxia-ischemia. *PLoS ONE*. (2013) 8. doi: 10.1371/journal.pone.0073031
40. Zwanenburg A, Jellema RK, Jennekens W, Ophelders D, Vullings R, Van Hunnik A, et al. Heart rate-mediated blood pressure control in preterm fetal sheep under normal and hypoxic-ischemic conditions. *Pediatr Res*. (2013) 73:420–6. doi: 10.1038/pr.2013.15
41. Eggink AJ, Roelofs LAJ, Feitz WFJ, Wijnen RMH, Mullaart RA, Grotenhuis JA, et al. In utero Repair of an experimental neural tube defect in a chronic sheep model using biomatrices. *Fetal Diagn Ther*. (2005) 20:335–40. doi: 10.1159/000086808
42. de Jonge P, Simaioforidis V, Geutjes P, Oosterwijk E, Feitz W. Ureteral reconstruction with reinforced collagen scaffolds in a porcine model. *J Tissue Eng Regen Med*. (2018) 12:80–8. doi: 10.1002term.2566
43. Vrancken SL, Nusmeier A, Hopman JC, Liem KD, van der Hoeven JG, Lemmon J, et al. Estimation of extravascular lung water using the transpulmonary ultrasound dilution (TPUD) method: a validation study in neonatal lambs. *J Clin Monit Comput*. (2016) 30:985–94. doi: 10.1007/s10877-015-9803-7
44. Alghrani A. *In Vitro Gestation I. In: Regulating Assisted Reproductive Technologies*. (2016). p. 109–43.
45. NIDCAP. Available online at: https://nidcap.org/ (accessed August 4, 2021).

**Conflict of Interest:** The work of MH, FD, LF, FN, MS, MV, and FV has been funded by the European Union via the Horizon 2020: Future Emerging Topics call FET Open, grant EU863087, project PLS, https://cordis.europa.eu/project/id/863087. MH, MV, and SO are shareholders in Juno Perinatal Healthcare BV, Netherlands. AP is Chair of Scientific Advisory Board of Concord Neonatal BV, for which he receives no compensation, https://concordneonatal.com. He also consults for Fisher and Paykel Healthcare and receives compensation https://www.fphcare.com/en-gb.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher’s Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.