Ethical Considerations for a First-in-Human Trial of Artificial Womb Technology

Food and Drug Administration hearing
Pediatric Advisory Committee
9/19/2023

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Yale-New Haven Children’s Hospital
Director, Program for Biomedical Ethics
Yale University School of Medicine
A brief overview of some of the ethical considerations...

1. Relevant ethical principles and guidelines
2. Patient/subject eligibility criteria
3. Terminology and moral status
3. Specific recommendations, and questions to be answered

Mercurio MR. *Pediatr Res.* 2018
Werner KM, Mercurio MR. *Semin Perinatol.* 2022
Dual laudable goals and possibly competing interests: Which way should the balance tip?

Vulnerable populations and the risk of exploitation

Image from
“Individual beneficence must take precedence over collective notions of beneficence, and the pediatric research community must remember that our responsibilities to individual children outweigh more speculative concerns about potential benefits to future generations of children.”

§ 46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

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• (b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
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HHS: 45 CFR 46 “Common Rule” (revised 2018): Additional Protections for Children as Subjects in Research

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Two research subjects

- Protocol could involve Cesarean delivery in a setting where it otherwise would not have been clinically indicated

- Risks to pregnant patient

- Risks to future pregnancies/newborns
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Ethical Considerations Regarding Artificial Womb Technology for the Fetonate

<table>
<thead>
<tr>
<th>Domain Name</th>
<th>Estimated Age</th>
<th>Prenatal Development Stage</th>
<th>Rationale for Upper Age Limit</th>
<th>Current Medical Support</th>
<th>Current Experimental Support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domain I</td>
<td>Fertilization &amp; Implantation</td>
<td>0 to 2 weeks (CA)</td>
<td>Zygote implants in uterus and becomes embryo</td>
<td>Limit set by regulation</td>
<td>In vitro fertilization</td>
</tr>
<tr>
<td>Domain II</td>
<td>Embryological &amp; Early Fetal Development</td>
<td>2 weeks (CA) to 21 weeks (EGA)</td>
<td>Embryological organogenesis followed by fetal development and growth</td>
<td>Infants born before 22 weeks EGA are generally considered to be non-viable</td>
<td>Non-existent</td>
</tr>
<tr>
<td>Domain III</td>
<td>Peri-Viability</td>
<td>22 to 25 weeks (EGA)</td>
<td>Fatal Growth and Maturation</td>
<td>Neonatal resuscitation, MV, NIV, surfactant, steroids, ECMO, TPN</td>
<td>AWT Liquid ventilation</td>
</tr>
<tr>
<td>Domain IV</td>
<td>Vulnerable Prematurity</td>
<td>26 to 34 weeks (EGA)</td>
<td>Fatal Growth and Maturation</td>
<td>Infants born after 34 weeks EGA have less risk of infant respiratory distress syndrome</td>
<td>Neonatal resuscitation, MV, NIV, surfactant, steroids, ECMO, TPN</td>
</tr>
</tbody>
</table>

Figure 1. Four domains of prenatal development and corresponding current medical support and experimental support. Legend: EGA, estimated gestational age; CA, conceptional age; MV, mechanical ventilation; NIV, Noninvasive ventilation; ECMO, Extracorporeal membrane oxygenation; TPN, Total Parenteral Nutrition; AWT, artificial womb technology.

- De Bie et al. Amer J of Bioethics 2023
Ethical permissibility, Domain III and parental choice

- The zone of ethical permissibility determined by **prognosis, feasibility, and relevant rights**
  - Mercurio and Cummings. *JPerinatol* 2020

- The “zone of parental discretion” (L. Gillam), aka “the gray zone”

- Thresholds often described in terms of gestational age
### Table 2. Survival of Infants Born at 22-28 Weeks’ Gestational Age in 2013-2018 for All Infants and Subgroups

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>All infants</td>
<td>22</td>
<td>23</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>No.</td>
<td>550</td>
<td>1083</td>
<td>1398</td>
<td>1604</td>
</tr>
<tr>
<td>Survived &gt;12 h</td>
<td>159 (28.9)</td>
<td>856 (79.0)</td>
<td>1298 (92.8)</td>
<td>1546 (96.4)</td>
</tr>
<tr>
<td>Survived to discharge or 1 y&lt;sup&gt;c&lt;/sup&gt;</td>
<td>60/549 (10.9)</td>
<td>535/1083 (49.4)</td>
<td>972/1391 (69.9)</td>
<td>1266/1599 (79.2)</td>
</tr>
<tr>
<td>Discharged home</td>
<td>56/549 (10.2)</td>
<td>520/1083 (48.0)</td>
<td>948/1391 (68.2)</td>
<td>1245/1599 (77.9)</td>
</tr>
<tr>
<td>Remained in hospital at 1 y</td>
<td>4/549 (0.7)</td>
<td>15/1083 (1.4)</td>
<td>24/1391 (1.7)</td>
<td>21/1599 (1.3)</td>
</tr>
</tbody>
</table>
Table 2. Survival of Infants Born at 22-28 Weeks’ Gestational Age in 2013-2018 for All Infants and Infants Actively Treated at Birth

<table>
<thead>
<tr>
<th>Survival</th>
<th>2013-2018</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No./total (%)</td>
<td>by gestational age, in weeks</td>
<td>22</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>All infants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td></td>
</tr>
<tr>
<td>Survived to discharge or 1 y&lt;sup&gt;2&lt;/sup&gt;</td>
<td>60/549 (10.9)</td>
<td>535/1083 (49.4)</td>
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<td>24/1391 (1.7)</td>
<td>21/1599 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Infants actively treated at birth&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>201</td>
<td>958</td>
<td>1369</td>
<td>1589</td>
<td></td>
</tr>
<tr>
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<td>159 (79.1)</td>
<td>856 (89.4)</td>
<td>1298 (94.8)</td>
<td>1546 (97.3)</td>
<td></td>
</tr>
<tr>
<td>Survived to discharge or 1 y&lt;sup&gt;2&lt;/sup&gt;</td>
<td>60/200 (30.0)</td>
<td>535/958 (55.8)</td>
<td>972/1362 (71.4)</td>
<td>1266/1584 (79.9)</td>
<td></td>
</tr>
<tr>
<td>Discharged home</td>
<td>56/200 (28.0)</td>
<td>520/958 (54.3)</td>
<td>948/1362 (69.6)</td>
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</table>
Canadian Neonatal Network 2010-2017 (all 30 tertiary NICUs)
Infants admitted to NICU not moribund (active Rx)

<table>
<thead>
<tr>
<th>GA (n)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 wk (85)</td>
<td>32%</td>
</tr>
<tr>
<td>23 wk (679)</td>
<td>50%</td>
</tr>
<tr>
<td>24 wk (1504)</td>
<td>69%</td>
</tr>
</tbody>
</table>

Shah et al. *J Pediatr* 2020
22 wk: survival at 3 years

- Neonatal Research Network, Japan
- 52 tertiary centers, 2008-2012
- Survival = 46% overall (125/271)
- Survival = 51% of those admitted to NICU (125/245)

- Kono et al. *BMJ Pediatrics Open* 2018
Survival to discharge:

University of Iowa 2006-2015 birth cohort *
Attempted resuscitation**

<table>
<thead>
<tr>
<th>GA at birth</th>
<th>Survival to DC</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 wks</td>
<td>64% (14/20)</td>
</tr>
<tr>
<td>23 wks</td>
<td>82% (41/50)</td>
</tr>
<tr>
<td>24 wks</td>
<td>89% (70/79)</td>
</tr>
</tbody>
</table>

*Specific protocols, high antenatal steroid use, special tiny baby teams

**No resuscitation attempted in: 2 pts at 22 wks, 2 pts at 23 wks, 0 at 24 wks

Nagano Children’s Hospital

- Nagano Children’s Hospital, Japan
- Single center, inborn 2011-2018

<table>
<thead>
<tr>
<th>Gest age</th>
<th>Survival (live born)</th>
<th>Survival (adm NICU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 wks</td>
<td>81% (13/16)</td>
<td>93% (13/14)</td>
</tr>
<tr>
<td>23 wks</td>
<td>93% (25/27)</td>
<td>93% (25/27)</td>
</tr>
</tbody>
</table>

- Yanagisawa et al. *Am J Perinatol* 2022
What current survival data should be used for determination of relative risk?

- The center where the AWT is to be trialed?
- US overall data (NRN data?)
- The centers with the best outcomes?
- Should we emulate centers with best outcomes before trying AWT?
Gestational age alone is a poor proxy for survival

- Intensive care for extreme prematurity – moving beyond gestational age.
  - Tyson and NICHD NRN. *NEJM* 2008

- NICHD outcomes estimator: GA, Wt, sex, antenatal steroids, plurality
  - Rysavy and NICHD NRN. *NEJM* 2015

... a better proxy for **prognosis** than GA alone
**Outcomes with conventional therapy**

*NICHD Neonatal Research Network (24 centers)*

2006-2012 birth cohort

<table>
<thead>
<tr>
<th>Gestation</th>
<th>Sex</th>
<th>Birthweight</th>
<th>Antenatal Steroids</th>
<th>Likelihood of Survival with Active Resuscitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 wk</td>
<td>male</td>
<td>500 gm</td>
<td>no</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22 wk</td>
<td>female</td>
<td>500 gm</td>
<td>received ANS</td>
<td>37%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23 wk</td>
<td>female</td>
<td>650 gm</td>
<td>received ANS</td>
<td>60%</td>
</tr>
</tbody>
</table>

**NICHD Extremely Preterm Birth Outcomes Tool**

[https://www.nichd.nih.gov/research/supported/EPBO](https://www.nichd.nih.gov/research/supported/EPBO)  acc 9/15/2023
Disability prevention with AWT

- Outcome is not only about survival

- Pulmonary morbidity and potential for prevention

- Neurodevelopmental impairment and potential for prevention
  - Short and long-term evidence
  - e.g., intraventricular hemorrhage diagnosed by ultrasound at 7 days vs cognitive function assessed at 7 years
Neurodevelopment impairment: Cognitive, CP, vision, hearing
22 wk: outcomes at 3 years

- Neonatal Research Network, Japan

- 52 tertiary centers, 2008-2012

- Survival = 46% overall (125/271)

- Survival = 51% of those admitted to NICU (125/245)

- 22 wks: NDI = 46%

- Kono et al. *BMJ Pediatrics Open* 2018
Disability among survivors  
University of Iowa    2006-2015 birth cohort

<table>
<thead>
<tr>
<th>GA at birth</th>
<th>No/Mild NDI among survivors (18 -22 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 wks</td>
<td>55% (6/11)</td>
</tr>
<tr>
<td>23 wks</td>
<td>68% (23/34)</td>
</tr>
<tr>
<td>24 wks</td>
<td>79% (42/53)</td>
</tr>
</tbody>
</table>

Risk of decisions based on early NDI outcomes

Developmental Follow-up of 200 VLBW newborns

Moderate to severe cognitive impairment
(MDI < 70 / MPC < 70):

20 months: 39%

8 years: 16%

- Hack et al. *Pediatrics* 2005

*But... a risk of later manifestations of other disorders*
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Parental permission/consent...

• Permission/consent often the setting of preterm labor, often in the setting of fear, exhaustion, urgency, and pain

• Aside from mode of delivery (pregnant patient gives sole consent), there are commonly two decision-makers for the newborn, for clinical and research participation. *Must both agree to the use of AWT?*

• *Whose permission is needed to withdraw*
What’s in a name?

• **Words Matter**
  - *What should we call the individual on AWT?*
  - Fetus? Neonate?
  - *Will this depend on gestational age (domain)?*

• **Moral Status**
  - How much an individual’s interests should count
  - *Legal, cultural, and ethical considerations*
Pushing back the gestational age threshold?

**Figure 1.** Four domains of prenatal development and corresponding current medical support and experimental support. Legend: EGA, estimated gestational age; CA, conceptional age; MV, mechanical ventilation; NIV, Noninvasive ventilation; ECMO, Extracorporeal membrane oxygenation; TPN, Total Parenteral Nutrition; AWT, artificial womb technology.

- De Bie et al. Amer J of Bioethics 2023
Lowering the threshold for attempted resuscitation: an ethical justification for refusal? (Domain II)

Two-Year Neurodevelopmental Outcome of an Infant Born at 21 Weeks’ 4 Days’ Gestation

Kaashif A. Ahmad, MD, MSc,a,b Charlotte S. Frey, MS, MPAS, PA-C,c,d,e Mario A. Fierro, MD,4,e
Alexander B. Kenton, MD,a Frank X. Placencia, MD4,e

PEDIATRICS Volume 140, number 6, December 2017:e20170103

- BW 410 gm: 21 weeks, 4 days by LMP, 21 weeks 2 days by 9 wk US
- Prolonged mech vent, BPD, ROP
- Discharged at 39+ weeks on nasal cannula O2
- 24- month follow-up: cognitive, motor, language Bayley III scores normal for 20 months corrected age.

- Though lowering the GA threshold is not the intention of AWT at present, a parent will eventually ask, and we should be prepared with an ethically defensible answer.
Ethical Challenges in first in human trials of artificial placenta and artificial womb

- **Recommendations:**

- **Collaborative informed consent:** research surgeon, neonatologist, MFM

- **Collaborative study design** between investigators, surgeons, neonatologists, MFM, bioethicists

- **Planning/discussion among stakeholders:** IRB, community stakeholders, parent representatives involved in discussion

  - Kukora et al. *Journal of Perinatology* 2023

  – A humble suggestion: a national conference on the ethics of AWT to include representatives from all of the above
Ethical Challenges in first in human trials of artificial placenta and artificial womb

**Recommendations:**

- Initial enrollment of very high risk (e.g., < 20% predicted survival)

- Gradually increase to include infants with a better prognosis (e.g., 20-50% survival) as a comparative effectiveness trial to conventional therapy, evaluating outcomes like survival and long-term neurodevelopment.

- Kukora et al. *Journal of Perinatology* 2023

**Fundamental questions:**

- What are the appropriate thresholds??

- What level of anticipated disability is considered worth the risk of AWT?
Selected References


- Flake AW, De Bie FR, Munson DA, et al. The artificial placenta and EXTEND technologies: one of these things is not like the other. J Perinatol. 2023 Jul 1. doi: 10.1038/s41372-023-01716-2. Epub ahead of print. PMID: 37393398.


Thank you