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Review article

Artificial placenta: Analysis of recent progress

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ABSTRACT

The artificial placenta (AP) has for many decades captured the imagination of scientists and authors with popular fiction including The Matrix and Aldous Huxley's "Brave New World", depicting a human surviving ex-utero in an artificial uterine environment (AUE). For scientists this has fascinated as a way forward for extremely preterm infants (EPIs) born less than 28 weeks of gestation. Early successes with mechanical ventilation (MV) for infants born above 28 weeks of gestation meant that AP research lost momentum.

More recently, the gestational age limit for survival now borders on 23 weeks and corresponds to the biological milestone of lung development marked by the early canalicular stage of lung morphogenesis. The so called greyzone of 23–25 weeks represents a steep increase in mortality with decreasing gestational age and current options in neonatal care are on the fringes of efficacy for this population. A shift in thinking recognizes the vitality of EPIs as a fetus rather than a 37–40 week neonate and this has reinvigorated the concept of the AP. This review will discuss the scale of extreme preterm birth with special reference to previable infants born in the greyzone. Recent AP studies using sheep models are compared, technical obstacles discussed and future research themes identified.

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1. Introduction

1.1. Border of viability

Premature birth is the early and often sudden delivery of a baby before 37 weeks of a normal 37–40 week term and is the second highest cause of infant deaths across the world [1]. The incidence of premature births in Australia and other developed countries is approximately 10% of all births annually. The mortality in the first year of life increases with decreasing gestational age at birth, as does both short and long term morbidity. Preterm delivery results in the interruption of pregnancy and fetal development. Approximately 45–50% of births are idiopathic and the premature rupture of membranes (PROM) accounts for 30% of all cases [2]. Risk factors include multiple births and maternal age over 34 [3]. Preterm delivery for advanced maternal age is in part due to the increased likelihood of other conditions (e.g. preeclampsia) predisposing them to preterm delivery [4].

At the lower end of the prematurity spectrum, mortality and morbidity is highest in extremely preterm (EP) infants (EPI) born less than 28 weeks or infants born with extremely low birth weight (ELBW) for gestational age (less than 1000 g). Further categorization distinguishes infants born under 6 months, between 22–24.9 weeks, as previable Table 1 [5].

Ultra extremely preterm infants or “micro-preemies” exist in a “greyzone” (GZ), often dying because their vital organs have not developed sufficiently to sustain life. Compared to the weight at term (3.5 kg), GZ neonates weigh approximately <400 g and <600 g at 23 and 25 weeks, respectively [8]. Defining the problem for developing countries is fraught with difficulty given the unavailability of reliable data for infant births less than 24 weeks, limiting this discussion to developed countries, [2]. The dilemma faced by neonatal intensive care units (NICUs) in developed countries is that the minimal survival using existing standards of neonatal care and the high risk of major morbidity may influence the decision to provide active intervention for infant less than 25 weeks. At the upper limit of this gestational range, infants receive active neonatal intensive care but this diminishes with decreasing gestational age [9]. Differences in hospital practice regarding the initiation of active treatment in part explain the variation in outcomes for EPIs [10].

The initial hospital costs for an infant born at 25 weeks was approximately USD 200,000 with estimates exceeding USD 1 million for GZ infants requiring long hospital stays [12,13]. In Australia, the burden of EP births is similar to other developed countries accounting for approximately 0.34% of all live births and this is on the increase [14].

1.2. Survivor morbidity

Survivors are at significant risk of developing severe short and long term health issues involving multiple systems, as the result of prematurity and mechanical ventilation (MV) associated injury Table 2.

1.3. Current treatment for extreme preterm infants

The current standard of neonatal care uses MV including:

- High flow nasal cannulae (HFNC),
- Intermittent mandatory ventilation,
- Continuous positive airway pressure (CPAP),
- High-frequency oscillator ventilation (HFOV) and
- High-frequency jet ventilation.

Surfactant therapy, developed in the 70 s assists lung ventilation by increasing compliance and steroids are used to accelerate fetal lung maturation. Together these innovations have extended fetal survival from 32 weeks to the current limit of 25 weeks [22,23]. In spite of the improvement to MV therapies there has been limited improvement to survival and no changes to short and long term morbidity for infants born in the greyzone [15,16].

1.4. Barrier to efficacy of mechanical ventilation

For infants born at a 37–40 week term, the first breathe inflates the collapsed lungs for the first time and closure of the fetal shunts diverts the flow of blood away from the placenta and toward the lungs, Table 3. This neonatal transition punctuates the start of postnatal life and survival requires the lungs to operate at full capacity [24–26]. The GZ period coincides with an important developmental milestone in lung development as the pulmonary

Table 1
Categories of preterm birth related to weeks of completed gestation and birth weight.

Degree of prematurity	Age range (weeks of gestation)	Birth weight (g)	% Survival (live births)	References
Preterm	<37		>98	[6]
Moderately preterm	32–37	1500–2500	>98	[6]
Very preterm	28–<32	1000–1500	95–98	[6]
Extremely preterm (EP)	22–<28	<1000	80–95	[5,7]
Ultra extremely preterm **“Greyzone”**	22–24.9	<600	2–20	[5,7]

Table 2
Survivor morbidity of extremely preterm infants.

System	Short term	Long term	Possible causality	References
Respiratory	Broncopulmonary dysplasia (BPD). Persistent patent ductus arteriosus. Respiratory distress syndrome.	Chronic obstructive pulmonary disease (COPD).	High pressure. MV. Increased intrathoracic pressure.	[15,16].
Nervous system	Intraventricular hemorrhage (IVH). Periventricular leukomalacia, white matter.	Cerebral palsy. Developmental delay.	High pressure. MV. Increased intrathoracic pressure.	[15,16]
Gastrointestinal	necrotizing enterocolitis.	–	Infection.	[17]
Visual	Retinopathy of prematurity (ROP)	Visual impairment.	High O_2 saturation.	[18,19]
Immune	Acute microbial infection. Sepsis.	Systemic infection.	–	[20,21]