Chapter 4 Artificial gestation

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Abstract

The idea of an “artificial womb” has been explored in literature, science fiction, and film for almost a century. Full ‘ectogenesis’ – growing a human from an embryo entirely within an artificial environment – might have profound implications for society, but is far from reality. However, recently published work with an animal model has described a technique for supporting extremely premature newborn lambs (equivalent to 23 weeks of human gestation) in a liquid environment with an artificial placenta for a period of up to four weeks. The apparent success of this model has led to suggestions that it could be trialled in humans in the near future.

If it were successful, artificial gestation might represent a paradigm shift in neonatal care. It could radically improve the prospects for infants born around the current borderline of viability. It may also shift the current threshold of viability and make it possible to save infants who could not be saved with current technology. However, artificial gestation will raise considerable ethical challenges – both during the first stages of its evaluation in humans, and,if successful in its application to neonatal care.

Key words

- Artificial womb
- Ectogenesis
- Ectogestation
- Viability

- Abortion
- Neonatal resuscitation
- Caesarean section

Introduction

Case

> It is the year 2030. Eleanor presents in preterm labour following a normal pregnancy at 21 weeks gestation. She is found to have cervical dilatation with bulging membranes, suggesting that delivery may be imminent. Eleanor and her partner are told that if she undergoes a vaginal delivery, even with the best obstetric and neonatal care the baby will die. However, a new technology has recently become available. It would involve having a Caesarean section to remove the baby before placing it in a liquid environment for at least four weeks, allowing its lungs and brain to mature sufficiently before a second 'birth'. Using this technique her baby will then have an outcome similar to those of infants born prematurely at 25 weeks of gestation. Most such infants survive, and the majority of survivors have no or only relatively minor long-term disability. On the down side, the process of Caesarean section at this gestation increases the chance of complications for Eleanor in future pregnancies (she is likely to need repeat Caesarean section, and has higher risks of bleeding or other serious complications such as placenta accreta or uterine rupture).

Should Eleanor consent to the procedure? What if she declines this intervention? This chapter will explore some of the ethical questions raised by a technique that we will call 'ectogestation'. These questions overlap with ethical questions raised by other advances in neonatal care.

We will start by describing the current state of scientific research into ectogestation. We will then set out some of the ethical questions raised by this technology and its application to neonatology. We will focus in particular on the question of 'viability' and the implications of ectogestation for both neonatal and obstetric management.

Definition

Several different terms have been used to describe technologies that aim to mimic the uterine environment for a fetus or embryo. These are often not clearly defined, leading to some confusion in the literature (Table 5.1). We will use the term 'Ectogestation' in this chapter to refer to techniques that aim to extend gestation by transferring fetuses to an artificial uterine environment.

Table 4.1. **Terminology relating to the artificial womb.**

Term(s)	Meaning in this review
Artificial womb OR Artificial uterus	Technology that aims to mimic the physical environment of the fetus within the uterus. This may allow conception and fetal development to occur entirely independent of a woman, or allow a fetus to be transferred from a woman's womb to an artificial womb at a certain point during pregnancy to continue gestation.
Artificial placenta	Technology that aims to artificially replace the extra-corporeal oxygen/nutrient exchange function of the placenta. Sometimes used interchangeably with artificial womb/ uterus in the literature.
Ectogenesis	Technology that would allow humans to be grown from embryos entirely in an artificial environment, without the need for a human womb at any stage.

Ectogestation* OR Partial ectogenesis	Technology that allows a fetus to be transferred from a woman's womb to an artificial womb at a point some way through pregnancy to continue gestation. This could be applied to infants who would otherwise be born extremely prematurely (and may not survive, or may suffer significant complications)

*This is the term and technology that will be the focus of this chapter.

Animal models of ectogestation

The first documented production of artificial placenta (in this case, to determine the effect of flow direction on the placental transmission) was published in 1946 [1] . To be successful, ectogestation would require alternatives to the amniotic fluid environment (sterile fluid incubation) and the umbilical placental system (blood circulation and gas exchange not dependent on fetal lungs) [2]. Several circuits have been tested on animal models, typically utilising Extracorporeal Membrane Oxygenation (ECMO) technology as the basis for the designs.

Some of the recent published attempts at ectogestation are summarised in Table 4.2. Although initial attempts had limited success (due to cardiovascular failure, hypoxaemia, sepsis etc.), these results have led to potentially more sustainable models, notably those by the paediatric surgery team at the Children's Hospital of Philadelphia [3, 4].

Table 4.2. **Published animal models of ectogestation since 2000.** Modified from Bird, 2017 [5] and Metelo-Coimbra, 2016 [6].

Group	Model	Survival	Mortality/ morbidity

Pak 2002 [7]	Goat	Up to 34 hours	Cardiovascular failure.
Reoma 2009 [8]	Lamb	4 hours	4 with hypoxaemia. 2 cardiac arrest. Congestive heart failure, high cannula resistance.
Arens 2011 [9]	Texel lamb	3 hours	Increasing resistance of oxygenator leading to decreasing blood flow rate.
Gray 2012 [10]	Lamb	24 hours	Hypoxaemia, cardiac failure, sepsis.
Miura 2012 [11]	Suffolk lamb	18.2 +/- 3.2 hours	Hypoxaemia, peripheral circulation failure.
Gray 2013 [12]	Lamb	70 hours	Hypoxaemia.
Rochow 2014 [13]	Piglet	4 hours	Hypotension and hypoxaemia with low flow rates.
Schoberer 2014 [14]	Texel lamb	3.22 +/- 1.89 hours	Hypoxaemia, respiratory failure.
Bryner 2015 [15]	Lamb	7 days	1 hypotension 2 arrhythmias. 2 device failure.
Miura 2015 [16]	Suffolk lamb	27.0 +/- 15.5 hours	Hypoxaemia, circuit clotting, circuit failure.
Miura 2016 [17]	Suffolk lamb	60.4 +/- 3.8 hours	Hypoxaemia, peripheral. Circulation failure.
Usuda 2017 [18]	Lamb	1 week	Euthanased after acute circuit failure in one lamb.
Partridge 2017 [3]	Lamb	4 weeks	See text.

CA = Carotid artery, UV = Umbilical vein, UA = Umbilical artery

Current state of science

In a landmark study [3], extremely premature lambs were delivered by Caesarean section at a level of lung maturity equivalent to 23 week gestation human infants. Blood vessels in the umbilical cord were connected rapidly to a low-resistance oxygenator circuit, which also provided artificial intravenous nutrition. The lambs were supported within a sealed fluid-filled bag (a “Biobag”), the fluid continuously exchanged to prevent infection. Eight of the lambs were sustained for between 20 to 28 days using this system, which researchers called the Extra-uterine Environment for Neonatal Development (EXTEND). A summary of the main aspects of the EXTEND are included in Table 4.2.

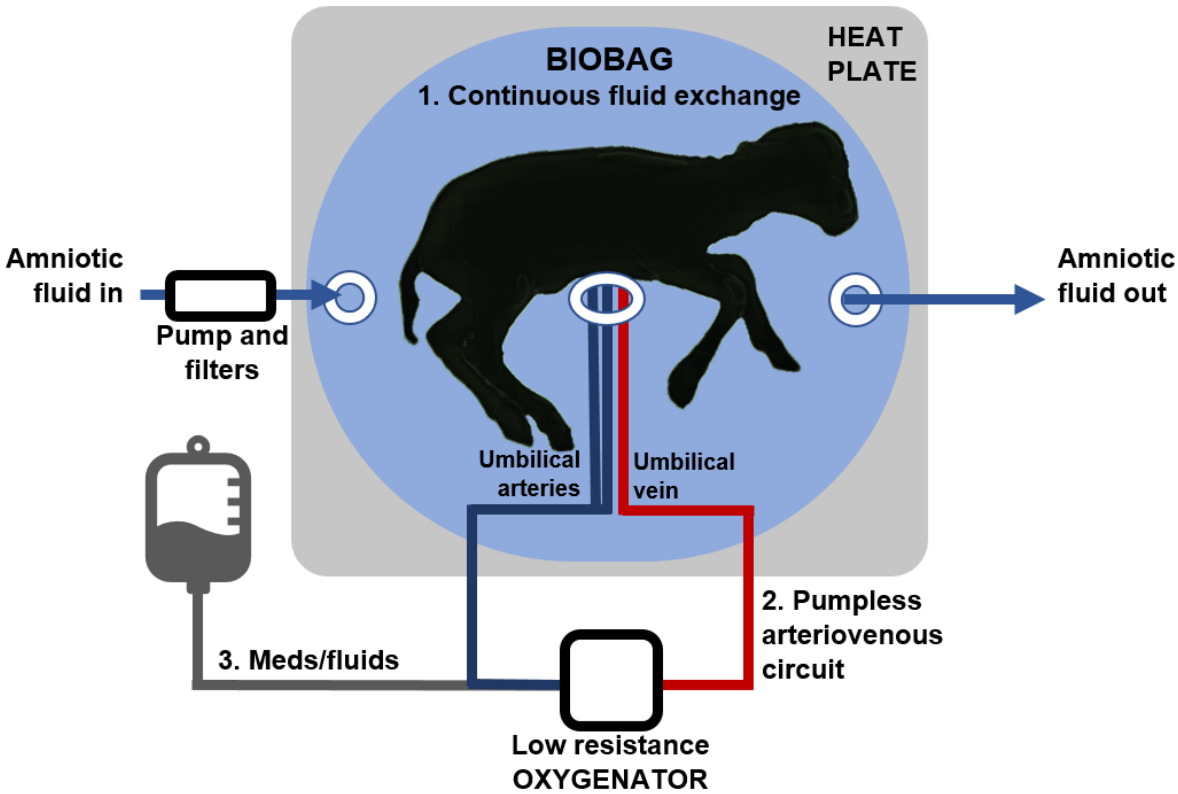

Figure 4.1. **The EXTra-uterine Environment for Neonatal Development (EXTEND)**. Shown here with umbilical artery/ umbilical vein cannulation. Adapted from Partridge, 2017 [3].

Table 4.3. **Aspects of the EXTra-uterine Environment for Neonatal Development (EXTEND), as described by Partridge, 2017** [3].

	Details of Philadelphia experiment	Effects
1. Continuous fluid exchange in a closed sterile environment	• The lambs were enclosed in a single use polythene bag constructed of a translucent, sonolucent and flexible film with multiple watertight ports. • The bags were placed on mobile support platforms that provided temperature and pressure regulation.	• The bag permitted monitoring, scanning and manipulation of the fetuses. • Continued development of the lambs' lungs by preserving the fluid-filled environment of the womb, resulting in equivalent development to age-matched controls based on early neonatal pulmonary function. • Reduced infection, and where low-level contamination did occur, this was eliminated by adjusting the fluid exchange rate and injecting antibiotics into the bag.

2. Pumpless arteriovenous circuit connected to umbilical vessels	• Fetal lambs were transferred directly from the uterine environment to the circuit. • The umbilical cord vessels were connected to a heparin-coated arteriovenous circuit where the blood flow was driven by the fetal heart. • The circuit priming volumes were within the normal range of placental blood volumes, and the blood was passed through a low resistance oxygenator.	• Preservation of fetal circulation. • No systemic anticoagulation. • No need for vasopressors. • No evidence of progressive acidosis or circulatory failure.
3. Medication and fluids	• Carbohydrates and amino acids with trace lipid were provided and titrated according to plasma levels of nutrients and waste products. • The final two lambs also received an insulin infusion.	• The lambs maintained stable metabolic parameters. • Insulin infusion permitted higher caloric loads and led to an increase in fetal growth.

Prior to the “Biobag” model, the researchers from the Children’s Hospital of Philadelphia attempted less successful open and semi-closed incubator designs which resulted in sepsis or bacterial overgrowth in half of the ten lambs [3]. In comparison, none of the thirteen “Biobag” lambs developed such complications. However, the “Biobag” was not without complication: two of the lambs experienced oxygenator failure and did not survive to delivery/ventilation; four of the lambs were shown to have pulmonary inflammation; and one had pulmonary hypoplasia. Cardiac failure had been a common problem in previous ectogestation experiments, however the Philadelphia group only observed hydrops in very early gestational lambs and saw no instances in “developmentally relevant lambs” beyond 105 days gestation. The majority of the “Biobag” lambs were able to transition to normal post-natal life, with apparent normal neurological outcomes. However, the researchers acknowledged limitations in the assessment of lamb neurologic function.

In another paper, the Philadelphia research group evaluated three different arteriovenous cannulation strategies: carotid artery/jugular vein, carotid artery/umbilical vein and umbilical artery (×2)/umbilical vein. [4]. Comparing circuit flow and pressure parameters across each cannulation strategy, the researchers found that umbilical vessel cannulation was the most successful, resulting in significantly superior flows and longer runs on the circuit. However, even in the umbilical catheterisation group, 3 died during cannulation, 1 had traumatic decannulation during the run, 1 had umbilical artery thrombosis, and 1 had iatrogenic air embolism.

The outcomes of these studies are promising; however clearly more research is needed before this technique can be applied to humans. Notably, developmentally-equivalent human fetuses are smaller than fetal lambs (0.5kg rather than 1kg), so questions remain as to whether this technology could be successfully applied to fetuses at the borderline of viability. Some of the limitations of the EXTEND technique are summarised in Table 5.4.

Table 4.4. **Limitations of the Extra-uterine Environment for Neonatal Development (EXTEND).**

LIMITATION	DETAILS
Contents of the amniotic fluid	The researchers utilised a simple electrolyte solution in this study which was lacking trophic factors (for example epidermal growth factor, which has been shown to have an effect on immature intestinal cells [19]) and other beneficial components of normal amniotic fluid.
Function of the placenta	The placenta has several functions, some of which have not been replicated with the Biobag e.g. provision of placental hormones, growth factors and maternal antibodies.
Contact from caregivers and parents	Although the Biobag does allow for monitoring through ultrasound and other techniques, it does not facilitate physical examination or affectionate contact from parents.
The need for Caesarean section	Caesarean sections at ~23 weeks of gestation currently involve major maternal risk*. It is unclear whether this system may be able to be used post vaginal delivery (for example, this would potentially stimulate transition to the post-natal circulation and reversal of those changes may be complicated).

Applicability in cases of chorioamnionitis	It is unclear whether it will be possible to clear infection in cases of preterm birth secondary to chorioamnionitis (an infection that is a common cause of premature labour [20]).
Applicability of animal model to humans – size of lambs	Human fetuses at 23 weeks of gestation are much smaller than developmentally equivalent lambs. When attempts were made with human-size equivalent lambs (480-750g) there were issues with excessive circuit flow, with development of hydrops and premature discontinuation (after 5-8 days) resulted [3].
Applicability of animal model to humans – intraventricular haemorrhage, uncertainty about developmental outcome	Lambs do not develop intraventricular haemorrhage, a common problem of prematurity in human infants [21]. Brain development in lambs also differs from humans.

***** At this gestation, the small uterus often requires a vertical incision rather than the transverse incision performed on women closer to term. This type of Caesarean increases maternal morbidity and has impacts on future pregnancies. One study showed the risk of uterine rupture after a periviable Caesarean was 4.5 times more likely than after a Caesarean at term [22].

Potential applications of ectogestation

In the future, ectogestation could have a range of clinical applications. The obvious direct extension of the animal model would be in infants who would otherwise be born extremely prematurely. Women in advanced preterm labour could choose to deliver their infant direct to ectogestational support – potentially extending gestation by a period of weeks, or maybe longer. The Philadelphia researchers claim that their “goal is not to extend the current limits of viability, but rather to offer the potential for improved outcomes for those infants who are already being routinely resuscitated and cared for in neonatal intensive care units.” As noted above, it is not clear whether it would be technically possible to use the biobag model in human infants before 22/23 weeks of gestation. However, it seems possible that with time the model might be applied prior to this point.

Ectogestation could be used in fetuses who have had premature rupture of membranes at extremely preterm gestation, where it might extend gestation but also reduce the risk of chorioamnionitis, and provide an environment more conducive to lung development – preventing or reducing oligohydramnios-related pulmonary hypoplasia and pulmonary hypertension. Similarly, in fetuses with renal conditions leading to anhydramnios or oligohydramnios, the Biobag might facilitate more normal lung development and allow neonatal survival (with adjunctive renal replacement therapy, similar to the reported use of amnioinfusion in fetuses with renal agenesis [23, 24]). Ectogestation might be used for other severe life-threatening congenital abnormalities as an alternative to EXIT-to-ECMO (where infants are delivered onto an ECMO circuit immediately at delivery). The Philadelphia group have used a version of their ectogestation circuit to provide low resistance extracorporeal support to lambs with a model of congenital diaphragmatic hernia [25]. The same researchers have suggested that Biobags could be used to deliver infants with congenital malformations (e.g. spina bifida) and perform correctional surgeries while maintaining lung development through liquid ventilation [3]. This might allow greater innovations or flexibility in fetal surgery (for example repeated surgery) with less risks to the mother.

Other, even more speculative applications could include ectogestation cases of placental insufficiency even when birth is not imminent, or the delivery of medical, stem cell or gene therapy directly to the fetus without maternal exposure.

Ethical questions

The first ethical questions raised by ectogestation will relate to its evaluation in early phase and then more clinical trials.

Ectogestation - research ethics

Who should be enrolled in trials?

While the animal studies of ectogestation have focused on a model of extreme prematurity, this may not be the best place for first-in-human studies. The first problem is that an acceptable outcome is possible with existing forms of support for extremely preterm infants. For example, at 23 weeks of gestation, there is approximately a 30% chance of survival if infants are treated actively, while 80% of survivors do not have severe neurodevelopmental disability [26]. While the outcome for a 23-week infant receiving ectogestation might be better than with standard care, the outcome may be significantly worse, raising the prospect of causing harm by enrolment in a trial. Infants of lower gestation (22 weeks or below) have lower survival chances with conventional care, but employing ectogestation may be more technically challenging (because of small physical size) and conflict with the stated goal of such therapy (ie not to extend 'viability').

Consent is crucial for clinical trials, particularly where the benefits of an intervention are unknown, and there may be significant risk. However, it could be ethically fraught to obtain consent for ectogestation from women facing extremely preterm delivery as there is sometimes little advance warning of delivery, and the risks to the mother (eg from classical caesarean section and an EXIT-procedure) may be significant. As with other fetal surgical interventions, such as surgery for spina bifida, ethics committees will need to decide what level of maternal risk is acceptable for possible fetal benefit [27].

As a consequence, the first human trials of ectogestation may be easier to justify in conditions like renal agenesis where fetal prognosis without intervention is extremely poor, there is potentially more time to obtain consent, and delivery could occur at a slightly later gestation, which would be technically easier and less risky for the mother. Alternatively, ectogestation might be used first in infants with such severe congenital abnormalities that they would otherwise be candidates for EXIT-to-ECMO procedures (eg very severe congenital diaphragmatic hernia/congenital heart disease), since such mothers would already be contemplating caesarean delivery and high risk extracorporeal support.

When would trials be ethical?

A second major challenge for trials of ectogestation will be the potential for loss of equipoise. When ECMO was first evaluated, there was intense ethical debate about whether it was ethical to randomise patients to standard treatment (without ECMO) [28]. If ectogestation is used for conditions with very high mortality (and appears to be successful), clinicians may lose equipoise rapidly. However, this could compromise the ability of researchers to evaluate the effectiveness of the new intervention. It may mean that other methods for evaluation are required (eg historical controls), that the evidence base for decisions about the use of the therapy is small, and that there remains uncertainty about the overall risks, costs and benefits of ectogestation.

Ectogestation – clinical ethics

If ectogestation appears to be effective in trials, its transition into clinical care is likely to be associated with similar ethical questions to other potentially life-saving interventions in newborn intensive care:

> Is this therapy in an infant's best interests (do the benefits outweigh the risks)?
>
> Does it represent a reasonable use of limited healthcare resources?

Both of these questions will be harder if the evidence base for evaluation is small, as may occur if trials are ceased early because of loss of equipoise. Questions relating to an infant's best interests are challenging since they require weighing up the harms of a potentially burdensome therapy (with potentially low chance of survival) against certain death without therapy [29]. If some or even all of the survivors have long-term morbidity or disability, the key ethical question is whether these are so bad that it would have been better for them to die [30]. If complications such as sepsis or intracranial haemorrhage, develop during the course of therapy, clinicians may feel that it would be better to withdraw treatment and allow the infant to die. However, as with other therapies in intensive care, that may lead to conflict in situations where parents strongly desire that treatment continue [31].

At this stage, it is unclear how much it might cost to support an infant using ectogestation. If ectogestation is a similar cost to existing technology, resource questions may be addressed similarly to current therapies in intensive care. In contrast, if ectogestation leads to prolonged support in intensive care for infants who would previously not have survived, that may require significant investment of resources in neonatal intensive care. There will then need to be careful ethical deliberation about whether this cost is justified. Should the cost threshold used for older patients be the same for therapies used to save fetuses [32]?

Some may have the view that fetuses have full moral status, and that therefore equivalent levels of resources should be expended to save them. Others may hold that it would be better to spend limited resources on saving or improving the lives of older children or adults.

A more distinctive ethical question could be raised by the effect of ectogestation on viability. Will ectogestation change the threshold of viability of extremely preterm infants? If so, what implications will this have for medical decision-making?

The concept of viability

In both obstetrics and neonatal care, the concept of "viability" is often taken to have ethical implications. In neonatology, resuscitation is considered to be an option if infants are 'viable', while in many jurisdictions, termination of pregnancy is either prohibited or limited beyond a gestation where the fetus would be 'viable' [33]. However, it is not always clear what exactly is meant by viability: is it the point beyond which survival of newborns is possible, or likely? Does it depend on whether technology or techniques required to save infants are available? Is it just a question of survival, or do infants need to survive without a certain level of disability?

Viability and neonatal care

In neonatology, there is not a single threshold of viability. Instead, there are at least two different thresholds – a level of maturity beyond which prognosis is sufficiently high that resuscitation is mandatory (the Upper Threshold), and a level of maturity below which the prognosis is sufficiently poor that resuscitation is not an option (the Lower Threshold) (see Figure 4.2). In between these two thresholds, resuscitation is seen to be optional (this is sometimes referred to as the 'grey zone').

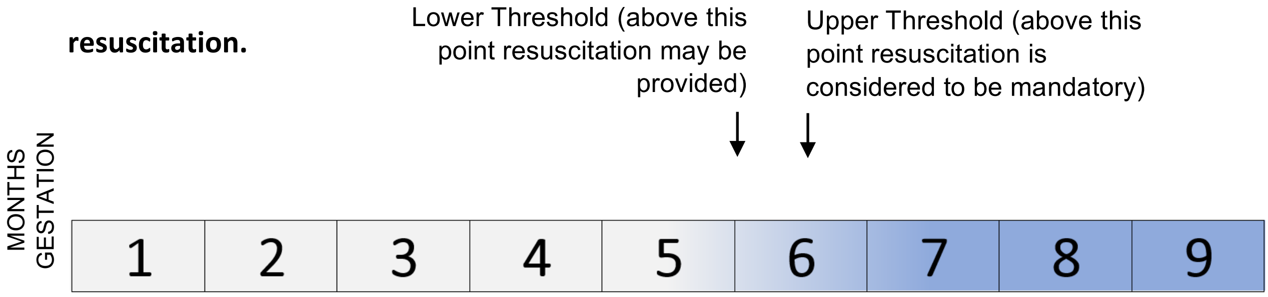

Figure 4.2 **Diagram illustrating thresholds for resuscitation.**

As noted above, ectogestation may make it possible for neonatologists to save the lives of infants who are more immature than those currently able to survive. This would potentially shift the Lower Threshold for neonatal resuscitation and expand the grey zone. It would not, however, necessarily shift the Upper Threshold, even if the outcome following ectogestation were shown to be excellent.

That is because of the requirement (as currently appears to be the case) for infants to be delivered by Caesarean section. In most jurisdictions, women are not obliged to undergo caesarean section, even if that would lead to the survival of a newborn – it would be regarded as an unacceptable breach of the woman's autonomy to perform a caesarean against her wishes [34]. Given that very early caesarean section, before development of the lower uterine segment, and caesarean section/anaesthesia for EXIT procedures are associated with higher maternal risks [35, 36], it appears that ectogestation should be regarded as ethically optional. Ectogestation is therefore somewhat different from other advances in neonatal care, which might improve outcome for extremely preterm infants without requiring any additional interventions or risks for the mother.

Viability and obstetric care

Some people, and some jurisdictions, consider viability important for the question of when termination of pregnancy is permissible. This position has been defended using several arguments. For example, some people believe that viability confers *moral status*, and therefore post-viability abortions are the equivalent of infanticide. Others maintain that doctors should be *consistent* in the way that they treat fetuses and newborn infants of the same level of maturity: once a pregnancy is sufficiently advanced that doctors would resuscitate premature newborns, abortion should no longer be permitted.

It is worth noting that many on both sides of the abortion debate reject viability as important for the permissibility of abortion. Those with strongly pro-life views argue that an early embryo has full moral status and therefore would disallow termination of pregnancy even before the point of fetal viability; those who are strongly pro-choice often believe that the ethical significance of a woman's autonomy means that termination should be an option even beyond viability. On either of these views, technologies that alter the point of viability (such as ectogestation) should make no ethical difference to policy or law around abortion.

For those who believe that viability is ethically important for termination of pregnancy, the relevance of a technique like ectogestation will depend on why viability is important and how viability is defined. For example, if ethical *consistency* is the reason why viability is important, that may mean that the Upper Threshold, and not the Lower Threshold of neonatal resuscitation is where the viability line should be drawn. In other words, termination of pregnancy should be limited or prohibited beyond the point in pregnancy where resuscitation of a premature newborn would be ethically obligatory. Since (as noted above) ectogestation is likely to remain ethically optional, it should not affect policy around termination,

Conclusion

Medical advances in neonatal intensive care have often raised challenging ethical questions. Future developments, whether they are small and incremental, or more revolutionary (as with the potential technique of ectogestation) will require clinicians to consider carefully whether or when those treatments should be used.

We have outlined some of the ethical issues that are likely to be raised if and when ectogestation is attempted in human infants. Clinical trials will need to consider when it would be ethical to perform trials, but also when such trials should cease. In translation to clinical care, it will be important to consider whether ectogestation is in the best interests of an infant, and also whether it represents a reasonable use of limited medical resources. Treatment advances around the borderline of viability are likely to be particularly controversial since they intersect with and potentially affect debate around the ethically divisive question of abortion.

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