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The artificial womb

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The availability of computer-controlled artificial hearts, kidneys, and lungs, as well as the possibility of implanting human embryos in *ex vivo* uterus models or an artificial endometrium, presents new perspectives for creating an artificial uterus. Survival rates have also improved, with fetuses surviving from as early as 24 weeks of gestation. These advances bring new opportunities for complete or partial ectogenesis through the creation of an artificial womb, one that could sustain the growth and development of fetuses outside of the human body.

Keywords: womb; artificial uterus; ectogenesis; embryo implantation; fetal surgery; assisted reproductive technology

Introduction

The mastery of *in vitro* fertilization and improvements in the survival of premature infants have opened new opportunities for *ectogenesis*, the implantation and full development of fetuses *in vitro*. Here, ectogenesis denotes the availability of an artificial uterus capable of fostering the development of embryos to viability.

An artificial uterus could assist women with damaged or diseased uteri by allowing them to conceive and carry infants, despite an inability to do so on their own. A second possibility is that an artificial uterus could serve as an incubator for preterm babies, specifically those who are delivered before approximately 24 weeks of gestation—the minimum for viability with current incubators. The development of such an incubator could provide a breakthrough for reducing fetal mortality and morbidity that stems from prematurity.

"Artificial wombs," as they are currently conceived, would function by connecting to an extracorporeal supply of maternal blood or replacement fluids. The artificial womb would supply nutrients and oxygen to an incubated fetus and would be capable of disposing of waste materials. This would, therefore, necessitate an artificial placenta for mediating the necessary exchanges between fetal circulation and the system that would replace the maternal flow.

The first attempts to support the implantation of human embryos outside of the human body were conducted in 1982 in Bologna, Italy, and continued at Mount Sinai Hospital in New York City in 1983; the first results were published in 1986.[1] The program of *ex vivo* human uteri maintained through extracorporeal perfusion led to different sets of experiments targeted at clarifying uterine physiology and pathophysiology.[1–6] The report of the first human embryo implantation in an *ex vivo*, isolated, extracorporeally perfused uterus occurred in 1989, stirring comments and bringing ethical concerns to attention, including those voiced by the editor of the journal *Fertility and Sterility*.[4] Ultimately, the experimental program conducted in Italy was stopped because of the ethical issues raised and the strong and vociferous opposition from the political community.[4] Further studies were conducted using the *ex vivo* model, however, not for studying embryo implantation. Rather, these studies investigated various pharmacological effects on uterine physiology. These included, for example, a set

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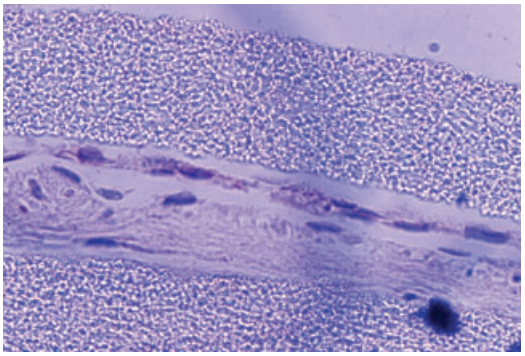

Figure 1. **The artificial endometrium obtained *in vitro* from epithelial cells placed on a bed of matrigel.**

of studies documenting the existence of a direct vagina-to-uterus transport called the "first uterine pass effect." This work details some important characteristics of the uterus, including the unexpectedly high levels of vaginally delivered hormones such as progesterone.[5,6]

The technology of *ex vivo* perfusion in human uteri was helpful in learning to imitate mechanisms governing human uterine receptivity and embryo implantation. Today, however, more advanced technologies are available and make possible the notion that an artificial uterus could support fetal development, at least for part of the pregnancy. Once perfected, however, an artificial womb would allow for the possibility to continue or initiate fetal development outside of the mother's body.

The artificial endometrium

Hung-Ching Liu, a researcher at Cornell University in New York, prepared a co-culture system that combined epithelial and stromal cells—a model reported as being the first step toward an artificial uterus.[8] Importantly, these experiments were not extended beyond the 6-day limit for embryo research enacted in the United States. As illustrated in Figure 1, several studies have employed artificial endometrium models and reported their responses to steroid hormones in various contexts.[9–12] In these co-culture systems, epithelial and stromal cells were layered on matrigel supports. This permits epithelial cells to exhibit spontaneous orientation and promising viability, allowing the development of new models for studying maternal–embryo interactions. Relatedly, in Japan in 1996, Kuwabara[9] reported attempts at preserving a developing goat for three weeks in an incubator that reproduced the uterus and placenta, together with amniotic fluid and blood supply. Similar attempts at developing an artificial womb took place concomitantly.

The artificial placenta

Placenta preservation through extracorporeal perfusion has been attempted in the past to study hormone metabolism and the respective fetal and maternal contributions to various pathophysiological issues.[7] For example, it has been demonstrated that the human placenta can still supply nutrients and dispose of waste products when connected to an artificial uterus.[6–19] However several attempts at uterine transplantation have taken place, but all were unsuccessful.[46,47] Placentation, or the passage of nutrients via the placenta, under these conditions remains an unresolved issue, in particular because of immunosuppressive therapies. It is possible that the placenta may offer immune protection to the fetus by passing antibodies such as immunoglobulin (IgG).[17]

Following the premature removal of the fetus from the maternal uterus, the three umbilical cord vessels could remain open by inhibiting their physiological occlusion, for example, through heparin flushing, placement of a stent, or by creating an arterial bypass that sustains exchanges between maternal and fetal blood.[20–23] A reservoir of maternal blood could therefore support placental physiology, provide nutrients for the fetus, and assure the removal of waste. Yet another option, where the artificial uterus and placenta would be directly connected to the maternal circulation, has been considered.[24,25]

Notably, the use of artificial "suppliers" and "disposers" has the advantage of allowing the fetus to develop in a separate environment where it is excluded from the possible deleterious effects of maternal disease, or from exposure to pollutants, alcohol, or drugs.[24,27–29] Furthermore, independent systems could not bear the risk of an immune reaction in the maternal system against the fetus because of insufficient gestational immune tolerance.

Additionally, waste disposal could also be achieved by dialysis. Oxygenation of the embryo or fetus has been achieved with extracorporeal membrane oxygenation (ECMO), a validated technique that has successfully allowed the development of a goat fetus for up to 237 hours in an amniotic tank.[30]

Current techniques are problematic, however, for providing proper nutrition. Total parenteral nutrition, as studied in infants suffering from severe short bowel syndrome, offers a 5-year survival of approximately 20%.[30–32]

Another potential application of ectogenesis is the possibility of xenopregnancy. Interspecific pregnancies (sometimes called interspecies pregnancies or xenopregnancy) involve an embryo or fetus and a uterine carrier belonging to a different species. Immunologically speaking, letting a fetus develop in a carrier of a different species is the equivalent of xenografts compared to allografts. Such an approach would put a higher demand on the gestational immune tolerance system to avoid immune rejection of the fetus. Furthermore, interspecific gestation would encounter issues linked to the different types of placentation that characterize each species. For example, the most invasive hemochorial placentation that characterizes humans implies a profound down-regulation of the maternal immune response. Conversely, the endotheliochorial type of placentation characteristic of cats and dogs, and those characteristic of pigs, ruminants, and whales, does not allow for true contact between maternal blood and the fetal chorion. Hence, interspecific pregnancies could bear the risk of generating inappropriate interactions between the fetal trophoblast and the endometrium of the mother.

In the case of an embryo from a Bactrian camel transferred to the uterus of a Dromedary, pregnancies can be carried to term with no other intervention beyond the embryo transfer.[47] The ability of one species to survive inside the uterus of another is often unidirectional—pregnancies are not necessarily successful in the inverse situation. For example, horse embryos survive in the donkey uterus, but donkey embryos perish in the uterus of an untreated mare.[48] Deer mouse embryos survive in the uterus of the white-footed mouse, but reciprocal transfers invariably fail. Ethical concerns are not considered here but would certainly arise if the development of human embryos were to be attempted in the uteri of other species.

The incubator

Although no technology currently exists for supporting the development of embryos from conception to viability, the importance of developing such technologies is now recognized. For example, new technologies have allowed our group to propose the computer-controlled sequence of two artificial kidneys: one provides the balanced fluid content of synthetic amniotic sacs, while the other permits the proper perfusion of the umbilical vessel with filtered blood coming from a reservoir of maternal blood. An artificial lung and heart and a temperature-controlled cabinet complete the system.[1–6] To replace placental function, an artificial placenta, or other filtering system capable of supporting nutrition, would be incorporated.

Discussion

In 2005, the French biologist Henri Atlan predicted in a book, *L'Utérus Artificiel*, that within 100 years, artificial reproductive technology would master the *in vitro* development of the human fetus. These approaches would offer the possibility of fertilizing oocytes and growing the resulting embryo to viability. This could also lead to treatments for certain anomalies *in utero* rather than after birth.[32,33]

Understanding the anatomical characteristics of the fetal–maternal interaction began several centuries ago—as shown in the famous drawing of an opened uterus with fetus *in situ*, *The Fetus in the Womb*, by Leonardo da Vinci—and the possibility of incubating a human fetus with an artificial apparatus has been a dream for many years. Interestingly, in 1932, Aldous Huxley wrote of a sort of artificial placenta in the novel, *Brave New World*, describing problems that later would be experienced by researchers attempting to develop an artificial placenta. It was not until the late 1950s, however, that actual efforts commenced for the development of the clinically applicable artificial placenta system.

Initial attempts to develop artificial placentas were abandoned in the mid-1980s. At the same time, however, continuous positive airway pressure (CPAP) systems and intermittent mandatory ventilation (IMV) using a mechanical ventilator were introduced to treat respiratory distress syndrome in premature newborns.[37–40] These new methods dramatically improved the prognosis of markedly premature newborns. More recently, a new system called extrauterine fetal incubation (EUFI), which used cannulation of the umbilical vein and artery that were connected to the circuit, was tested on a baby goat that was ultimately extracted by cesarean section at 148 days of pregnancy.[40–44]

In contrast to the pessimistic view of the feasibility of partial or complete ectogenesis, we believe that the following lines of research provide evidence to suggest that improving technology may advance this goal: our model of extracorporeal perfusion of the human uterus that allows for embryo implantation that is operational for up to 52 hours;[1–6] the achievements of Hung-Ching Liu at Cornell University, permitting the development of an artificial human uterus using endometrial cells grown over a uterus-shaped scaffolding (the scaffolding dissolves as cells grow and form novel uterine tissue);[8] and the experiments conducted by Yoshinori Kuwabara of Juntendo University supporting developing goats with an artificial placenta and uterus.[9] Though no experiments have yet been conducted on human fetuses brought to term, experiments on previable goat fetuses have resulted in maintenance of life for several weeks outside the uterus.[14,15] However, issues related to nutrition and hormonal stability in these models remain.

In our view, liquid ventilation constitutes the next important step in the treatments of premature infants. In 1989, the first human studies offering liquid ventilation to infants, with no chance for survival through conventional therapy, were performed.[14,17–45] The results were promising and larger trials are now under way. Recently, a fluorocarbon liquid was developed that has the capacity to carry a large amount of dissolved oxygen and carbon dioxide.[17–45] By inserting liquid into the lung, Shaffer and his colleagues argue, the lung sacs can be expanded at a much lower pressure. Thus, the development of liquid breathing could serve as an intermediate stage between the womb and breathing in open air.

In conclusion, we foresee that partial ectogenesis—the growth and development of fetuses between 14 and 35 weeks of pregnancy—is within reach given our current knowledge and existing technical tools.

Conflicts of interest

The authors declare no conflicts of interest.

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