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From the maternal uterus to the "uterus device"? Ethical and scientific considerations on partial ectogenesis

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Abstract.: The article aims to elaborate the progress made in partial ectogenesis research on sheep as well as human embryos. Since the ban on embryos experimentation after the 14-day window is a major roadblock in terms of partial ectogenesis research, the authors have weighed the possibility that such a ban could be reconsidered. In favor of easing such a restriction, it may be argued that: (a) unlike the Catholic approach, prevalent ethics precepts hold that the embryo's interest ought to be balanced against the interests of the other parties involved; (b) an extension of the 14-day deadline would no longer make ethically untenable practices acceptable; hence, the "slippery slope" argument, although generally worthy, would not conclusively apply to partial ectogenesis; (c) in mainstream embryo research efforts, there is a conflict between the lives of embryos and the health of individuals already born; as for partial ectogenesis, however, such a conflict would be between the lives of embryos and the lives of fetuses which would not survive otherwise. Still, in light of the embryo's status as a human being, the authors conclude that such research practices should only be allowed on supernumerary embryos.

Key Words:
Partial ectogenesis, Artificial uterus, Pre-embryo, Embryo research, Slippery slope argument.

Introduction

In the 1980s, *in vitro* fertilization techniques have made it possible to have embryos develop outside of the maternal womb, to be later transferred into the womb till birth. Scientists believe that in the foreseeable future, pregnancies may develop entirely outside of the maternal womb through the technique named ectogenesis. Embryos would be fertilized *in vitro*, and then transferred into a machine that would serve as the maternal womb, by fulfilling all necessary biological processes and functions, thus allowing embryos to fully develop into fetuses and then to be born[1-3]. Such a breakthrough technology would constitute a third stage in human procreation; scientists have long been working on making such a scenario into a reality, with very promising results[4,5]. Several arguments are commonly used either in favor or against ectogenesis. Detractors have indicated a major cause for concern: granted that pregnancy outside of the maternal womb becomes technically possible, what guarantees that children thus born will not suffer from psychological and cognitive consequences? It is a question well worth asking, since ectogenesis experts themselves have had to admit that they still do not have a thorough understanding of the processes and mechanisms by which a fetus undergoes its development in the womb. Furthermore, the needs of any fetus change and evolve throughout gestation, according to hormonal patterns that are still not fully understood, and only the maternal organism is apparently capable of adapting to and meeting such needs. The maternal placenta, for instance, has such a complex array of functions that it is extremely difficult to reproduce artificially[6]. Given the necessary conditions that make childbirth possible, any attempt to achieve pregnancy outside of the maternal body will inevitably become a risky experiment on human life itself, which could lead to children being born with psychological and intellectual issues. Such children would in fact be deprived of vital chemical and emotional influences that the maternal

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system exerts on the fetus throughout gestation. Still, it is worth noting that the same concerns and doubts had been expressed before *in vitro* fertilization procedures started being used. At the time, some had concerns about the normal development of children born through such techniques. Nonetheless, such children do not present higher rates of anomalies than children conceived and born naturally. As for children who may be born through ectogenesis at some point, it is necessary to assess the risk that they may suffer from mental and psychological abnormalities. Preliminary research trials are of little value in that respect since it is obviously not possible to assess the mental and psychological well-being of children prior to their birth. Hence, a vicious circle may develop: it is not morally and ethically acceptable to carry out experimentation on the birth of a child from an artificial uterus until it is reasonably proven and guaranteed to be safe. At the same time, there is no way of proving safety until the technique is carried out in trials. The only way to break such a vicious cycle is, according to Singer and Wells[7], to anticipate the moment in which premature children can be saved. Such a gradual process would allow for constant supervision and monitoring of outcomes in progressively more premature children, ensuring survival and a good level of life quality for such children. Such a path would still be long and hard, certainly taking years; it could however lead to the point where a human embryo, produced by *in vitro* fertilization, could be kept alive without having to be transferred into the maternal womb: that would lead to a safe and effective ectogenesis[7]. Artificial gestation could then be achieved through gradual improvements in neonatal intensive care.

Results

Complete and Partial Ectogenesis

Ectogenesis may comprise two distinct approaches: "complete" ectogenesis and "partial" ectogenesis. The former would likely lead to a major shift in how maternity is viewed from an anthropological perspective. Complete or full ectogenesis in fact entails the complete gestation of a fetus in an artificial "uterus", completely divorced from the maternal body as we know it. Such a technique would therefore enable biologically sterile couples to have genetically related offspring, making the controversial practice of surrogacy obsolete. It would however have another advantage as well: allowing fertile women to have a biologically related child without the need to ever have a pregnancy; that would make women more similar to men in that regard[8]. "Partial" ectogenesis, on the other hand, entails the removal and transfer of a fetus from the mother's body into an artificial uterus to complete the gestation process. Such a technique has medical applications. Firstly, it could contribute to lowering the risk of miscarriage, thus saving the lives of embryos. It would also allow for the constant monitoring of embryonic development, in order to select the most viable ones to be transferred into the maternal womb and brought to term. Moreover, the artificial womb could be used to make prenatal interventions that surgeons currently have to postpone till after birth; such operations could be carried out by temporarily removing the fetus from the mother's womb, keeping it alive in the artificial one for as long as necessary to perform the intervention, and then transferring it back into the mother's uterus. Another key factor should be taken into account: not only is Artificial Womb Technology (AWT) capable of keeping a fetus alive till birth, but it would also enable women to rely on an alternative to pregnancy without the risk of losing it. Partial ectogenesis, for instance, would make it possible for seriously ill women (e.g., with cardiovascular or neurological conditions), for whom traditional pregnancy would be extremely high risk, to achieve parenthood and have biological children. Women likely to develop conditions such as gestational hypertension or HEELP syndrome, which involves Hemolysis, Elevated Liver enzyme levels, and Low Platelet levels. Such patients could otherwise decide to give up on their pregnancies, but their fetuses could have a chance to survive by being transferred into the artificial womb and complete its development till birth. In addition, partial ectogenesis could be a valuable tool for women who have no major health condition, and still want to prevent symptoms such as pregnancy-related nausea. Another scenario may also arise: a pregnant woman has no intention of having a child[9]. Partial ectogenesis would make an abortion no longer necessary: the fetus could be removed from the mother's womb and transferred into the artificial one, where it could fully develop. After birth, it may then be adopted. Arguably, partial ectogenesis may allow women to pursue their parenthood plans in the ways and forms that they freely choose[10,11].

Research on Sheep Embryos

Premature fetuses are likely to have major health issues, which likelihood gradually subside as the moment of birth approaches[12-16]. Current research aims to devise a valid alternative to current incubators in order to prevent or minimize complications associated with extremely preterm births, limit the damages that occur as a result of life support procedures and foster the children's physiological development. Scientists have conducted research on both animal and human embryos, hoping to soon be able to carry out such procedures on severely premature babies[17]. In 2017, British researchers[18] engineered and built an extra-uterine life support system, or "biobag", which looks like a containment sack filled with electrolyte solution (designed to mimic amniotic fluid) through micropore filters and has an umbilical cord connected to the fetus. The biobag has been designed to pump blood, oxygen and nutrition necessary for embryo development and to dispose of waste materials. The internal temperature is kept constant and in check at all times. The fluid environment is totally sterile. In order to assess the biobag's degree of effectiveness, neonatologists have used 8 lambs, prematurely born via cesarean section after 110 days of gestation, roughly the equivalent of 23 or 24 weeks for a human pregnancy, i.e., the shortest possible term at which a fetus can have a chance to survive out of the womb. The fetuses were then transferred into the artificial womb, where they spent 28 days. No relevant differences were observed by researchers between the lambs that developed in the biobag, and their counterparts developed in the mother's uterus[19,20]. Nonetheless, they acknowledged that the device needs further improving, and that their conclusions need independent validation. However, the research team concluded that the system can be deemed ready for human testing. In 2017, a research team of Japanese and Australian scientists[21] used the Ex-vivo Uterine Environment (EVE) platform for the development of lamb fetuses at 95 gestational days. The results however proved to be disappointing, with higher than average rates of morbidity and mortality[22]. The authors reconfigured and published the study 2 years later, in 2019, and released its results showing higher survival rates and demonstrating "the potential clinical utility of a further refined EVE therapy system to improve outcomes for extremely preterm infants"[23]. The EVE study[24] found an 87.5% survival rate, with a significant incidence of brain damage and early signs of liver dysfunction. Ultimately, such studies are quite interesting, despite their limitations. The artificial devices have only been tested on small samples over too short periods. Further research is therefore essential prior to human testing, since there are still overwhelming challenges to overcome. The research is currently ongoing. The European Union has allocated 3 million Euros for a project undertaken at the Eindhoven University of Technology[25], seeking to develop an artificial womb, designed and engineered as a perinatal life support for the survival of premature babies born before the 22nd gestational week, which would normally make survival all but impossible. No information is currently available as to the design of the new artificial womb; it appears certain, however, that it will not be meant for full ectogenesis, since current level of scientific knowledge does not allow that. Before testing such devices on premature human fetuses, neonatologists will have to investigate the possible consequences that may arise from the placement of human fetuses into the artificial womb, in terms of infections, for instance, which are often the direct cause of preterm births[26]. Another issue worth exploring is about the long-term consequences of having lived and developed in an artificial uterus: even when human testing becomes an option, babies will have to be monitored over a long period of time, at least two years, in order to verify whether the artificial womb may indeed be a better solution, as many hope, than traditional incubators currently used in neonatal intensive care wards, not only in terms of mere survival rates, but also taking into account physiological issues commonly linked to preterm births.

Scientific Research and the Use of Human Embryos

In 2016, two British[27] and American research teams (in Cambridge, London and The Rockefeller University, New York)[28] created an environment that replicates the human uterus. Ninety-one human embryos were used, which were donated by their intended "parents" to scientific research after assisted reproduction procedures. The researchers have focused on figuring out what happens in the first 13 days of embryonic life, at the blastocyst stage, i.e., from conception to the lodging of the embryo in the maternal uterus (at around the 6th-7th day of life). The scientists have allowed the embryos to develop on a sort of artificial, transparent plastic uterine wall, which they were able to document graphically in all

various phases of the development process. They have been able to witness the embryonic evolution, which grows from 100 cells in the 5th day to over 900 in the 13th day. It has been observed that in the 5th -6th day, the embryo's structure looks a bit like a football, with a smaller sphere inside which will later become, almost entirely, the fetus: the external cells will eventually form the extra-embryonic tissues, which will develop into the placenta and the yolk sack. Between the 8th and the 10th day, the embryo forms two cavities, which give way around the 12th day. As the scientists have pointed out, that might depend on the fact that the support created to replicate the uterine wall was flat. Hence, even at this early stage of development, human embryos can normally grow even without relying on any maternal "intervention", unlike what was previously believed. The study has also kept track of all morphological and molecular changes undergone by embryonic cells in real time, as well as all their interactions until the 13th day of development. The capability of embryos has been observed to self-organize in structures that appear very similar to those visible after implantation in uterus. Scientists are hopeful that they will be able to take their research to the next level, by reproducing tridimensional substrata where embryos can implant, and see how it all proceeds from there. An attempt may also be made to introduce nutrients in the artificial environment, in order to keep the embryos alive. Experiments such as this are crucial for a different reason as well: they make it possible to find various differences between the development patterns of human and mouse embryos over a 13-day period, particularly from the standpoint of cell organization. The study's ultimate result has indicated that in order to gain a thorough understanding of embryonic development, it is necessary to use human embryos[29]. It is quite noteworthy that the scientists have been able to keep the embryos alive for 13 days, whereas prior to this experiment, embryos outside of the uterus had only been cultured for 9 days at most, and more typically for only one week[30]. Still, the experiment had to be ended, since it is only legal to perform research on embryos within 14 days of fertilization.

The Warnock Commission and the 14-day Limit

Back in 1984, the Warnock Commission set a 14-day limit to carry out research on human embryos[31,32]. The Commission coined the term "preembryo" to indicate such embryos on which research is allowed. Preembryo in fact refers to the period of development that begins with fertilization and ends with the appearance of the primitive streak fourteen days later. Preembryo had an ethical and political valence, since it represented the time limit set between acceptable and unacceptable research practices[33]. The Commission has set the 14-day limit, because as mentioned earlier, that is when the "primitive streak" appears, i.e., a precursor of the brain and the spinal cord. The "primitive streak" also marks the beginning of the process named gastrulation, when three layers of germ cells differentiate (namely endoderm, mesoderm, and ectoderm). Such a process marks the latest time in which the embryo could cleave into twins (i.e., twinning) or in which two embryos could merge into one (e.g., tetragametic chimerism)[34]. Even more importantly, the Warnock Commission has asserted that no definitive stage in embryonic development is more significant than another: all in fact constitute parts of a continuous process which depends on the accurate timing of each sequence. It has therefore been concluded that there is no stage of development that can signal when an embryo should not be kept alive. Undoubtedly, the overall scientific scenario back in the 1980s was profoundly different from the current one. The underlying issue back then was whether to legally allow embryo research beyond the 14 days following fertilization; nevertheless, it made no sense to do so, since scientific technologies did not allow scientists to keep embryos alive for any longer than a few days. The Commission report therefore was not aimed at setting a strict limit which was absolutely not supposed to be breached. The 14-day rule has been codified into the Human Fertilisation and Embriology Act of 1990[35], and it is still in force in the statutes of 12 other world nations (such as Canada and Spain) and is indicated in the guidelines adopted by other 5 countries, among which Singapore, China and the United States[36]. Nowadays, scientists believe that being able to observe embryonic development beyond the 14th day from fertilization may be instrumental in shedding a light on complex processes such as tissue formation and even on the root causes of miscarriage. Moreover, extending the 14-day limit could enable researchers to learn how to keep embryos alive *in vitro* for longer. A 2020 research study[37] has proven that embryo research can be implemented with promising results up to 13 days following fertil-

ization; it has therefore been requested by many specialists that the time limit be extended to 28 days. Research findings have in fact shown that at 28 days of development no functional neural connections or sensory systems exist yet[38]. Furthermore, the first stages of differentiation of neurons with synaptic formation usually develop from the early 6th week to the late 5th (after 34-36 days); it is therefore unlikely for a potential nervous system framework to even exist any earlier than the 7th or 8th week of embryonic development. By virtue of that, there should be no downsides about extending the time frame for embryo research from the current 14 to 28 days, or even longer than that. Further studies could let scientists figure out all aspects of earliest human development with a high degree of accuracy. Newest technological advancements such as bioprinting 3D will likely go a long way towards achieving that[39]. This would most likely be a giant stride towards the development of the artificial uterus. Still, it is essential to establish whether such an extension would be ethically acceptable.

Discussion

The Embryo's Moral Status

The complex, multifaceted issue of embryo status, which has sparked broad debates about its nature and identity[39], first came to the fore when assisted reproductive technologies became available. Such a discussion has however become even more relevant when issues such as the use of embryos for research purposes, the fate of hundreds of thousands of stored embryos or the 14-day rule had to be confronted[36,37]. As for the divisive topic of embryo status, we are still nowhere near finding a shared solution. Three distinct positions clash on that subject: the "secular" one, which is in favor of embryonic stem cell research because it views embryos as simple "pools" of cells, mere biological material with no rights prior to childbirth. Those who espouse that line of thinking point to the potential benefits that embryo research may yield, such as a much greater understanding of early human development and more effective *in vitro* fertilization techniques and infertility treatments (including fertility-sparing interventions[41-43]), in addition to still experimental surgical options such as uterine transplantation[44,45], which is itself highly controversial from a moral and ethical standpoint[46-48], but still entails an actual womb being donated for transplantation[49,50] into a woman suffering from absolute uterine factor infertility (AUFI)[51]. Such techniques are likely to evolve further, as bioengineering of tissues and organs lays the groundwork for a major breakthrough in transplantation medicine[52] through organogenesis, *in vivo* regeneration and regenerative immunology[53]. Aside from the new bioethical quandaries likely to arise, there is no doubt that making such therapeutic options safer and more reliable would greatly benefit infertile couples both physically and psychologically[54-57]. Moreover, the supporters of free and unfettered embryo research stress that embryos have the mere potential to become a human being, but they are not there yet, and that is enough for all limitless human embryo research to be allowed[58]. That reasoning represents a utilitarian approach that seeks to frame bioethical issues not according to universal respect for all life forms, but only in terms of individual or collective interest. Consequently, the "weak", such as embryos, patients in a vegetative state or the terminally ill, risk being discriminated against. The Catholic stance, on the other hand, views embryos as on a par with human beings, from the moment of conception onward. The moment when birth occurred does not affect the intrinsic moral value of embryos, which is the value bestowed upon them by God regardless of whether they were already born or were still at the stage of fertilized eggs. Hence, in keeping with that precept, destroying an embryo is tantamount to committing a homicide, from a Catholic moral perspective. An intermediate position may also be identified: the one that acknowledges the human nature of embryos although without going so far as to consider them human beings. Those who subscribe to such beliefs do recognize the embryo's right to life and not to be subjected to research practices in the interest of others; still, embryo destruction is not conflated with murder. According to such a balanced approach, the embryo's interest needs to be balanced against the interests of couples and ultimately, society at large[59,60].

The Slippery Slope Argument

Some have argued that extending the 14-day limit for embryo research may lead to a slippery slope. Such an argument assumes that legalizing a certain practice "x" (such as the extension of the 14-day term) would set in motion a process by which unethical and unsound practices "w",

"y" and "z" would also end up being allowed (such as paving the way for research practices on fetuses or even infants). The slippery slope argument thus manifests a fear that once a certain rule or law has been changed, it will be easier to make more changes, and harder to keep things in check constantly[61]. According to that line of reasoning, the 14-day limit should therefore not be extended, since that would make it harder to draw the line between moderately controversial practices such as research on pre-embryos, and highly contentious ones, such as experimentation on fetuses at advanced stages of development. As for the 14-day rule specifically, some fear that the term will progressively be extended even further, as scientific progress continues[37]. Singer and Wells[7], for instance, have expressed concerns about the possibility that embryos may be kept alive as sources of living tissue and organs, to be used for transplants. A major issue with organ transplants is in fact transplantation rejection, which occurs when the organ recipient's immune system recognizes the donor organ as foreign and attempts to eliminate it. Embryo research could ultimately lead to embryos being used for transplants. A necessary precondition for the removal of non-reproducible organs (such as heart and kidneys) from a deceased donor is the donor's brain death. Only the total absence of brain functions can in fact allow for the removal of organs from the donor's body. In the case of embryos, organs may be taken before the brain has even started functioning. Singer and Wells[7] have based their thesis on the fact that embryos cannot feel pain and suffering until their central nervous system is developed. Hence, embryos could be made to develop in an artificial womb, and then use their organs for transplants as soon as they have become viable. We feel that the slippery slope argument, albeit valid in some respects, is somewhat ineffective when it comes to embryos. A mere extension of the time frame within which embryo research is allowed, in fact, would certainly not make research on fetuses, or harvesting them for organs, any less unacceptable. Undoubtedly, the slippery slope patterns can be avoided by putting in place substantial penalties, proportionate to the degree of gravity of any given violation, against researchers who undertake illegal trials and experiments. Imprisonment, fines or exclusion from access to public funding and/or the withdrawal of permissions to conduct research may all be proportionate and effective deterrents. The meaningful case of He Jiankui comes to mind: a Chinese scientist who allegedly achieved the birth of two genetically altered babies and was heavily punished for it[62].

Conclusions

Human embryos have dignity because they embody the beginning of human life itself; they can therefore not be degraded as if they were nothing more than genetic waste material. On the other hand, partial ectogenesis has the potential to save the lives of countless embryos. A somewhat peculiar scenario emerges by virtue of that. Usually, in fact, embryo research is aimed at finding new forms of treatment for patients already born; nonetheless, partial ectogenesis may benefit fetuses, i.e., humans at the prenatal stage of development. That differentiation does not change, however, the ethical quandaries arising from such practices. Such embryo research is in fact conducted in the interest of future entities, rather than to benefit the embryo on which such research is undertaken. That aspect should necessarily affect the moral judgement. It is in fact objectionable to give up on the opportunity to save future fetuses, i.e., human lives, in order to avoid sacrificing embryos. It is necessary to strike a balance between the lives of embryos and the future lives of fetuses, not between the lives of embryos and the health and well-being of people already born. That is however not enough to justify the production of embryos for research purposes, but it could lead to allowing research on supernumerary embryos, i.e., embryos left over from *in vitro* fertilization practices. Such embryos, which will never be used for reproductive purposes, are destined for life-long cryopreservation and storage. By virtue of the principle of beneficence, it would be preferable to use them for research that might benefit millions of new fetuses, as opposed to a frozen non-existence devoid of any prospect. Still, it is necessary to find solutions in order to ensure a well-balanced and sensible use of embryo research, while staving off any arbitrary and unchecked exercises[63].

The authors believe that given the new opportunities and challenges brought about by technological advancements, it is incumbent upon lawmakers to shed a light and identify which paths should be undertaken. Before that, however, it is vital to have thorough and well-focused debates within the global scientific communi-

ty on embryo research. Such a complex issue needs to be regulated with the highest degree of caution and responsibility. Different opposing positions and views in a democratic and diverse setting are bound to conflict and often clash. When vital issues such as birth, death, and the disposability of one's own body are on the line, agreements and disagreements on each side of the issue will inevitably surface. The citizenry also needs to be called upon and get involved by expressing a view on the numerous issues caused by almost boundless technological progress. The manifestation of the people's will should only come after a thorough public information campaign on a national and international level, which should involve ethicists, scientists and jurists. Such initiatives would be helpful to both national communities, enabling them to express informed preferences, and the international community as a whole, in order to find shared solutions. It is ultimately up to lawmakers to strike the right balance between two fundamental values: respect for the life of embryos, even supernumerary ones, and the needs of scientific research, by taking into account the prevalent approaches in civil conscience and determining reasonable conditions on which research and experimentation can be feasible. Progress in embryo research may relatively soon lead to the realization of a "uterus machine", a device that will allow for the growth and development of thousands of severely premature children, saving them from certain death or from an unhappy life scarred by irreversible brain damage.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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