

Letter to the Editor

Comment on the article by Zaami S, et al. “Advancements in uterus transplant: new scenarios and future implications”. Eur Rev Med Pharmacol Sci 2019; 23: 892-902

Dear Editor,

We have carefully pored over the article titled “Advancements in uterus transplant: new scenarios and future implications”, published in the European Review for Medical and Pharmacological Sciences journal¹. The article broaches a particularly compelling topic, especially at a time when technological advancements in biomedical research have seen extraordinary developments, even more so as it pertains to assisted procreation techniques. Cryopreservation of gametes and embryos has greatly contributed to medically-assisted procreation worldwide, although it is not devoid of risks²⁻⁴. Assisted fertilization procedures have come to supplement, and at times replace, natural conception. Very often, in fact, pregnancy is achieved through the *in-vitro* fertilization of embryos in specialized laboratories; that gives rise to a sort of “autonomy” of such embryos, which become separate entities from women’s bodies: at that stage, embryos are in fact akin to mere “products”, manipulated and kept alive by very specific technical intervention^{5,6}. Such developments have engendered a wide array of complex ethical, medical, psychological and even legal issues, thus fostering a confrontation among diverse interests and rights, which are bound to clash, all involved in the procreation process: the parents’, the children’s, the gamete donors’ and the family members. All such potentially conflicting elements have been regulated in Italy by law n.40/20047. Embryos become “children” only when they are finally implanted into the wombs of intended mothers following homologous or heterologous fertilization procedures⁸⁻¹².

Medically-assisted procreation is closely linked to uterus transplantation. In the late 20th Century, a medical team of Swedish specialists from Goteborg laid out a surgical pattern that eventually enabled a woman born without a womb to undergo *in-vitro* fertilization before having a donor uterus implanted¹³. Obviously, uterus transplantation will not help women with a functioning uterus who for various medical reasons, cannot become pregnant or homosexual males seeking parenthood¹⁴. Despite indisputable progress, uterus transplantation is still at the experimental stages, presenting unique issues and complexities¹⁵. Patients need to undergo immunosuppression treatments entailing serious risks, such as reduced kidney functions, bone damage and diabetes. Fetuses growing in transplanted wombs are at risk as well: premature birth and low birth-weight have been observed. In order to be deemed eligible for transplantation, patients should be capable of producing a number of embryos, which will be frozen and implanted into the transplanted uterus at least a year later¹⁶. That process is meant to ensure that the transplanted womb expands and grows along with the fetus. Cesarean birth is generally opted for, in order to prevent excessive childbirth-related stress¹⁷.

Uterus transplantation can be carried out *inter vivos*, from live donors, or from deceased ones. In cases of transplantation *inter vivos*, the surgery is usually even more complex, due to the extreme difficulty that comes with separating arteries and aortic veins that nourish the organ itself. In such instances, the surgery and anesthesia last longer, which may damage the ureters that interwoven with the veins and arteries. Extensive counseling is absolutely necessary for women who decide to undertake such a problematic surgical path, in order to verify whether such patients are psychologically prepared to undergo an utterly

complicated surgical operation and receive a uterus donated by another woman. Patients need to be aware of and willing to accept the considerable physical burdens that donors must bear. Ideal donors are often found in the recipient's mother or sisters who already have children of their own and are willing to selflessly donate their wombs for the purpose of making it possible for their family members to achieve motherhood¹⁸. Although uterus transplantation is not a "reproductive" form of transplantation (no gametes are in fact, donated), it enables recipients to bear children. Hence, uterus donors may get the idea that they are the real mothers of the children eventually born. Psychological counseling ought to closely focus on that risk. It is also essential for recipients to fully understand that they will have atypical pregnancies, at best. Firstly, the nerve endings of transplanted uteri will not be reconnected, making it impossible for the recipient to feel any contraction or fetal movement inside the womb; on the other hand, hormone-related morning nausea and fatigue will be felt. The inability to feel contractions and movements might cause the patient to grow "estranged" from the transplanted organ, and to feel it as not her own¹⁹.

Ectogenesis, on which scientists have been working for many years, may soon become a valuable substitute for uterus transplantation. Such a technique allows for a fertilized oocyte to develop until the fifth day after fertilization (at the blastocyst stage) and then be implanted into a device designed to artificially reproduce membranes and exchange mechanisms in order to ensure placental functions and viable amniotic fluid and uterine walls that normally host embryos in natural pregnancies²⁰.

At the time being, the beginning and the end of a pregnancy, i.e. till the fifth day and after the 24th week following fertilization, can already run their course outside the maternal body. After the 24th week, premature babies continue developing inside incubators, through which they are provided intensive care that is, however, not necessarily successful in averting seriously and even irreversible brain anomalies, mostly due to poor oxygenation of the baby's still underdeveloped lungs.

Total ectogenesis should be able to span roughly six months, the time between the fifth day after conception and the 24th gestational week. A viable artificial uterus is still far from being achieved²¹. Nevertheless, a spirited debate is ongoing among scientists as to the advantages as well as the contraindications, whether medical and ethical, of human ectogenesis compared to traditional gestation. Ectogenesis, in fact, entails an anthropological transformation of the very notion of motherhood, creating a dichotomy between the woman and the fetus, while depriving her of the gestational experience altogether²².

Medical considerations speak in favor of ectogenesis, e.g. the opportunity to preserve embryos from miscarriages, or enabling women born with no uterus, or who had it removed due to illness, or those suffering from cardiological or neurological conditions, to become mothers too; it could also allow for the transfer of fetuses into artificial uteri in cases of serious complications striking the mother, such as gestational hypertension. Artificial wombs will have to guarantee an adequate degree of protection against viruses and bacteria; such technology will undoubtedly need to evolve as the fetus develops. Fetal needs, in fact, evolve and change throughout the pregnancy based on hormonal mechanisms that are as yet little known, and only the maternal organism is capable of effectively meeting such needs²³.

Should scientists eventually figure out the inner workings of such a complex machine, ectogenesis could definitely become a valuable alternative to surrogacy, a somewhat controversial practice, both ethically and legally, by which a surrogate mother agrees to have an embryo implanted into her uterus and to carry the pregnancy to term on behalf of commissioning parents^{24,25}. Ectogenesis could potentially stave off the numerous issues arising from surrogacy. Surrogate mothers, for instance, might decide to refuse to hand over the child to the commissioning parents or could consume alcohol, take drugs or take up eating habits that might harm the fetus²⁶. From such a perspective, it would be far preferable to implant the embryo into an artificial womb, which provides constant support and care, as well as continuous monitoring, rather than rely on a surrogate mother, who cannot be supervised and who might even turn into a threat for the fetus.

Nonetheless, from a scientific standpoint, it appears to us extremely risky to keep experimenting towards the artificial womb. Such a machine, in fact, could allow the fetus to develop, but it will not be likely to ensure that the soon-to be child gets all the nutrients it needs, which only the mother can guarantee. Artificial wombs will probably lead to a completely artificial gestation, but an utterly manipulated one²⁷. Science is still unaware of the unique bond that is formed between mothers and the fetuses developing in their wombs; therefore, we still ignore how such relationship plays a role in shaping

maternal and child well-being even after delivery. Scientists, for instance, know how the children's immune system first starts developing in their mothers' wombs and keeps doing so during breastfeeding. In both cases, mothers and children establish an interaction physically as well as psychologically. When children cry, for example, that stimulates the production of maternal milk, and its composition varies depending on the duration of breastfeeding, the mother's eating habits, her psychological state, and the antibodies found in her immune system²⁸. The emotional and psychological relationship between a mother and her child, which grows and develops during gestation in uterus is also still quite undefined²⁹. Fetal neurological development is profoundly affected by early sensory experience; hence, the absence of maternal heartbeat itself could give rise to complications in fetal development³⁰.

Modern science does not know the necessary conditions for children to be born healthy. For that reason, any attempt to carry a pregnancy to term outside of the maternal womb is tantamount to experimenting with human life, which risks turning into a reckless trial, since it might lead to innumerable children poised to live unfortunate lives. Provided that humans tend by their very nature to seek ever greater knowledge, we ultimately believe that pushing the boundaries beyond the pillars of Hercules would be unacceptably risky.

Conflict of interest

The authors declare no conflicts of interest.

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G. Montanari Vergallo, C. Ciallella

Department of Anatomical, Histological, Forensic and Orthopaedic Sciences, "Sapienza" University of Rome, Rome, Italy