EDITORIALS

Uterus transplants in India: yawning regulatory gaps

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The hubbub following the first two uterus transplants in India seems to have died down. But it highlights gaps in the mechanisms to regulate potentially harmful research. It also flags the need to examine this controversial technique which is poised to become part of the assisted reproductive technology industry in India.Though an experimental and risky procedure, with many ethical concerns, uterus transplant is being presented here as an established practice. It is being offered as an opportunity to have a biologically related child while bypassing the limitations of surrogacy, enabling "legal, biological and gestational motherhood" (1).

Uterus transplants have been conducted so far on women who do not have a uterus, or who have a uterine condition that rules out their gestating a pregnancy. Once the transplant is confirmed as successful, pregnancy is established through in vitro fertilisation. The recipient woman must take anti-rejection drugs until the uterus is removed, which is once she achieves the desired number of childbirths, or if the transplant fails.

An experiment and with risks

There is no doubt that uterine transplant is at an experimental stage.Though 25 women have undergone uterus transplants worldwide since the first one in 2000, only a trial in Sweden has reported successes so far: nine women received a transplant and six children have been born so far; two of the transplants failed(2). Other trials are reported as planned or on-going in Japan, France, the UK, the US, Australia (3), Italy (4) and Czechoslovakia (5).

The risks of uterus transplant will become apparent only in the years to come, though some can be anticipated based on the procedures used. The transplant recipient, a healthy woman, in the course of three major surgeries and one or more pregnancies is exposed to the possibility of life-threatening infections, damage to internal organs, blood clots and bleeding, kidney failure, ovarian hyper-stimulation syndrome, diabetes, reduced bone density and cancer. The risks to the foetus include congenital malformation, low birth weight and pre-term labour (6). The long-term psychological impact is unknown.

Trials in some countries use, or plan to use, only deceased donor transplants but the Swedish programme relies entirely on living donor transplants, and a few other programmes are expected to do so as well (3). The uterus and the ovary are the only two organs to have received ethics approval for live donations for a "quality of life" (as opposed to life saving) improvement to the recipient (3).

Harvesting of the uterus for transplantation from a live donor is more complex than a hysterectomy, which itself is not a low-risk operation. In order to ensure proper blood supply to the transplanted uterus, a larger section of blood vessels must be taken along with the uterus. This entails major surgery under anaesthesia, of 10-13 hours, with all the attendant complications. The Swedish surgeons acknowledge that the surgery subjects the donor to "substantial surgical risk" (7).

The phantom regulators

With its massive assisted reproductive technology industry, India was bound to look at uterus transplants which are predicted to be part of standard practice in the next few years (7). In addition to the risks, there are other questions, including how it would be used in a society in which women face pressure to give birth to a biologically-related child. It is unfortunate that such research is currently free from most regulation. But as the apex body governing health research, the Indian Council for Medical Research (ICMR) could at least have brought together ethicists and civil society organisations to develop research guidelines much before the first transplant in India.

If uterus transplant was an established therapeutic procedure, it would be regulated only under the Transplantation of Human Organs and Tissues Rules (THOTA). THOTA's rules govern, among other things, permissions for live and deceased donation, and the certification of hospitals in which transplants may be carried out (8).

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However, there is no body in India charged with regulation of uterus transplant as research. The office of the Drugs Controller General of India (DCGI) must give approval to certain types of drug trials, and the Health Ministry's Screening Committee (HMSC) must review and approve international collaborative research. The ICMR's ethical guidelines apply to all health research including that which is governed by the DCGI. In the case of uterus transplant, by convention, the ICMR would be responsible for developing ethical guidelines on uterus transplant research, and such research would be required to be reviewed and monitored by the institution's ethics committee. However, neither the ethics committee nor the ICMR has the authority to take any substantial action against violations in such trials; nor is compensation required for participants who are injured or die in such trials. The Medical Council of India has the power to suspend the licences of doctors who violate research guidelines and, consequently, the Code of Medical Ethics (9: chapter 7, para 7.22) but this has rarely happened.

This gaping hole in the regulatory structure was evident in 2016 when an orthopaedic surgeon announced a study of whether stem cells could revive the brain dead. While the DCGI stated it had no guidelines or requirements on testing stem cells on the brain dead, the ICMR said the trial was both unscientific and unethical, but admitted that it could do nothing. The ICMR was similarly helpless about the misuse of stem cells as therapy (10).

Approvals inadequate and flawed

The first uterus transplants in India were done in a Pune hospital in May 2017 by an onco-surgeon assisted by a cardiac transplant surgeon. The Pune hospital obtained approval for therapeutic transplants (11), and certification as a transplant hospital, under THOTA (12). However, the surgical team did not include a surgeon with the THOTA-specified "one year training in the respective organ transplantation as an active member of team in an established transplant center;" (8: Para 26C(b)) – among the requirements for certification as a transplant hospital. The ICMR's director general said uterus transplant was a "grey regulatory area" (13).

In response to an application under the Right to Information Act, the ICMR revealed that a Bengaluru clinic's research proposal was reviewed by the HMSC. The HMSC, which is constituted by the Ministry of Health and Family Welfare, is supposed to screen and approve international collaborative research that is submitted to the ICMR. The ICMR granted permission for a trial of two transplants (14). The Medical Council of India granted a temporary permit to the Swedish transplant surgeon to conduct the transplants at the Bengaluru clinic (15).

However, the ICMR's responses seem to violate key ethical and procedural requirements. For one, the HMSC requires applicants to explain the project's relevance to "national health priorities" (16); uterus transplant certainly is not a national health priority. Second, the HMSC accepted the clinic's institutional ethics committee's approval, instead of sending the proposal to its central ethics committee specifically charged with reviewing proposals forwarded to it by the ICMR. However, the ICMR chose not to do so. Third, the proposal should have met the ICMR's ethical guidelines on transplant research that live donations may be only of "renewable tissues … which on removal will not greatly alter, physiological functions", and with "… the extenuating circumstances being the saving of another human life" (17: Page 78). And finally, the ICMR has stated that the trial would be monitored by "the Ethics Committee and as per the guidelines of the DCGI", though the DCGI has no authority for non-drug research. The project name and details are not available on the ICMR's website. There is no mention of the Bengaluru clinic's IEC on the website of the DCGI.

The ICMR's lack of transparency also raises questions. It refused to release a copy of the Bengaluru clinic's application-related documents –including the approvals of the ethics committee and other regulatory bodies, information on previous research, expert opinions, and the informed consent form. The last was refused "because of the issues related to Intellectual Property Rights" (14). It is not known what intellectual property rights could be contained in an informed consent form that would be given to all the women in the trial.

Some questions the ICMR should have considered

A few questions should have been debated and decided on, with the participation of civil society organisations and ethicists, before permitting uterus transplants in India, even as research.

In the last decade non-lifesaving transplants have been done of the face, hand, larynx, penis, and uterus for quality-of-life benefits (18). The claim that uterus transplant improves quality of life has been disputed by the International Federation of Gynaecology and Obstetrics (FIGO) in a 2008 statement (19) that has not been updated since. Before embarking on uterus transplant in India, an evaluation should have been done of its risks against the expected improvement in quality of life.

Assuming that uterus transplant is justified, should there be any restrictions to its use? As a reference point, one could look at the criteria drafted by a group of researchers at McGill University in Canada for the ethical feasibility of uterine transplantation (20). The Montreal criteria recommended that given the current level of research, uterus transplant should be restricted to a "genetic female" of reproductive age, with no medical contraindications to the procedure; for whom transplant was the only option; who desired it specifically in order to gestate a pregnancy (and therefore for transient use), for whom there was a "personal or legal

contraindication to surrogacy and adoption", who has no "psychological comorbidities" that could interfere with the procedure, who is not obviously unfit to be a mother, and who can give informed consent and follow the doctor's orders. The donor must be healthy, have given a declaration that she has completed childbearing, and be able to give voluntary informed consent (21). Are these criteria reasonable and are there conditions in which they could change in the future? Is it possible, for example that medical eligibility for uterus transplants expands over the years, as has happened with in vitro fertilisation as well as kidney transplant?

If uterus transplant is justified, should uterus donation be restricted to deceased donors or is live donation permissible? So far, the only successful transplants leading to childbirth have been from live donors. The success rate of live transplants is possibly because a uterus transplanted from a live donor has greater likelihood of success (3). However, some programmes are restricted to deceased donor transplants. A trial in Czechoslovakia reports both live and deceased donor transplants (5). The transplants in Pune were from live donors, as will be the transplants planned in Bengaluru.

FIGO has described the use of live donors as "ethically inappropriate" because of the risks to the donors (19: p 85).

The ART industry in India has a well-documented history of unethical practice and a healthy dislike of regulation. Thousands of women will have benefitted from these technologies. But many more will have suffered temporary and sometimes permanent harm by various drugs and procedures -- to have a genetically related child, for the sale of ova, and as surrogates. The industry has exploited the social pressure on women to have a genetically related child or face stigma and violence and possible abandonment, thriving on their vulnerability while glorifying motherhood. Barely a month after the Pune transplants, some 150 women are reported to have put their names down for the procedure (21).

In such an environment, it is unlikely that women will be able to make a truly informed decision on whether or not to risk their health and even life for a chance for "legal, biological and gestational" motherhood. It is more than possible that women for whom a uterus transplant is "medically indicated" will face pressure to undergo the procedure. It is also more than possible that family members can be coerced into donating their uterus, possibly even for payment.

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