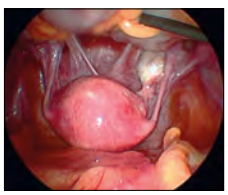
Uterus transplantation from a deceased donor



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Since 2015, when the first livebirth after uterus transplantation from a live donor was published in *The Lancet*,[1] at least ten other livebirths have been reported in scientific journals[2,3] or in the general media. This is the result of an acceleration in the number of uterus transplantation procedures that have been completed in the past 3 years, with 50 procedures being done since then, both from live and deceased donors (appendix).

One of the challenges that needs to be addressed is to define inclusion criteria for donors and recipients on the basis of results of the procedures that have been carried out so far. A balance between maximising success, minimising risk for the patients involved in the procedure, and maximising the organ availability should be achieved. In a context in which the scarcity of human data is still the norm, the report by Dani Ejzenberg and colleagues in *The Lancet*[4] reveals a breakthrough in the field of uterus transplantation. They report a healthy livebirth, representing the proof of concept of the functionality of uteri procured from a deceased donor. In this case, the donor was aged 45 years and affected from a subarachnoid haemorrhage. The recipient was 32 years and suffered from Rokitansky syndrome, with an agenesia of the distal vagina but without any kidney or musculoskeletal malformations. The ovarian reserve of the recipient was normal as proved by the generation of eight good-quality embryos in one in vitro fertilisation cycle. The surgical approach differed from the previous successful cases with living donors in that the venous outflow was duplicated, through the uterine and ovarian veins compared with the exclusive use of uterine[2] or ovarian veins.[3] Ejzenberg and colleagues also have shown that the human uterus can remain functional after cold ischaemia of four times longer than the average time after live donation (7 h 50 min *vs* 1 h 18 min;[5] appendix). The authors also challenged the principle of waiting at least a year after transplantation before attempting pregnancy by doing the embryo transfer earlier. Although there are enough data in the literature suggesting that the perinatal outcome could be impaired during the first-year after transplantation of solid organs,[6] one has to bear in mind that the adverse perinatal outcome could be related to the severe underlying condition motivating the transplantation and not to the transplantation itself.[7]

According to the staging system for the assessment of surgical innovations developed by the IDEAL framework,[8] uterus transplantation is on the second step of five (2a-development). This means that the procedure is still in the early stages of refining and many questions are still unsolved. For example, the technical effectiveness of the different aspects of the uterus transplantation technique should be compared in future studies: approaches (live *vs* deceased donation), surgical techniques (open *vs* laparoscopic retrieval of the uterus), type of vessels used for anastomosis (internal iliac branches *vs* ovarian *vs* both), immunosuppression protocols and adjuvant therapies before or after the procedure (and before or during pregnancy). The postoperative control should be standardised and the external validity of the timing and scoring of the rejection scales should be assessed. The impact of new technologies such as preimplantation genetic screening on the time to pregnancy, successful pregnancy, and miscarriage must be assessed. Potential iatrogenic interventions such as planned preterm deliveries should be discouraged. Also, long-term outcomes of the offspring need to be recorded.

Once the technique is more standardised, indications should be explored in more controversial groups of uterine infertile patients potentially benefiting from uterine transplant, such as patients with non-operable fibroids, patients having received pelvic radiotherapy, or those with unexplained implantation failures. With increasing indications, more uteri will be needed and there will be room for exploring new sources of uteri, especially bioengineering, which will not be fulfilled even with the use of organs from deceased donors.

All in all, the research to be done in this field (whether from alive or deceased donors) should maximise the livebirth rate, minimise the risks for the patients involved in the procedures (donor, recipient, and unborn child), and increase the availability of organs. With the expansion of the field, the number of procedures will increase, and this will allow the community to set different types of study designs, such as comparison studies (ideally randomised) or long prospective series. In an expanding field such as uterus transplantation, the role of collaborative networks and societies such as the International Society of Uterus Transplantation or new interest groups in already existing scientific societies will

For the **International Society of Uterus Transplantation** see www.isutx.org

be crucial. They should promote education and guidance so that the groups performing uterus transplantation for the first time can benefit from the experience of the pioneers. They should also encourage forthcoming procedures to be done and reported in a transparent way by endorsing prospective registration of the procedures and by developing accurate registries.

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Fibroblast growth factor 21 for non-alcoholic steatohepatitis

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Non-alcoholic steatohepatitis is a form of fatty liver disease that is characterised by hepatic necro-inflammation, progression of fibrosis, and a strong association with metabolic syndrome, and is increasing as a cause of morbidity and mortality. In the USA alone, 27 million people are anticipated to have non-alcoholic steatohepatitis by 2030, which is expected to cause 105 430 cases of decompensated cirrhosis, 12 240 cases of hepatocellular carcinoma, and 78 300 deaths from liver-associated causes annually.[1] Although a reduction of 10% bodyweight with lifestyle interventions can effectively reverse fatty liver and even liver fibrosis, most patients cannot achieve or maintain this degree of weight reduction.[2,3] Unlike other diseases of a similar magnitude, there is no registered pharmacological treatment for non-alcoholic steatohepatitis. Four drugs have now entered phase 3 development, with trials reporting their histological outcomes in the next 2–3 years.[4]


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In *The Lancet*, Arun Sanyal and colleagues[5] report the findings of a phase 2 study that evaluated the safety and efficacy of two doses of pegbelfermin (BMS-986036)—10 mg once a day and 20 mg once a week, given subcutaneously—relative to placebo for 16 weeks in 75 patients with biopsy-proven non-alcoholic steatohepatitis. Pegbelfermin is a pegylated analogue of fibroblast growth factor 21 (FGF21). FGF21 is a protein produced by the liver, adipose tissue, and pancreas that has variable effects in animals, including reducing sugar intake, increasing insulin sensitivity, browning adipose tissue, and increasing energy expenditure.[6] In animal models[7] of non-alcoholic steatohepatitis, FGF21 reduced hepatic lipotoxicity and improved liver injury, potentially due to increased adiponectin concentration or a direct hepatic effect. Phase 1 trials[6] of FGF21-class molecules in obese or overweight patients with type 2 diabetes have shown favourable effects on weight, circulating lipids, and adiponectin concentrations, providing the rationale to examine their effect in non-alcoholic steatohepatitis.

In the study by Sanyal and colleagues,[5] pegbelfermin treatment led to a greater absolute reduction in hepatic fat fraction relative to baseline, as measured by MRI; this difference was –6·8% in the 10 mg daily pegbelfermin