absence of LH, FSH stimulation enhances P synthesis in the granulosa cells. Once pregnenolone is converted into P, the latter cannot be further metabolized to androgens (Miller, 2008). Therefore, it is possible that even in the event of a low response, P can reach high serum concentrations at the end of stimulation, especially if the patient has received high doses of FSH, due to overstimulated granulosa cells activity with no LH activity compensation.

We acknowledged the possibility that the impact of high P on cycle outcome could be related to the embryo but suggested more evidence points to a detrimental effect on the endometrial receptivity. This was already suggested by previous results from our group (Melo et al., 2006) finding no negative impact of oocyte donor P levels on recipients pregnancy rates. More recently, we have demonstrated an altered gene expression profile on the endometrium at day hCG + 7 (i.e. the implantation window) when P was >1.5 ng/ml (Martínez Conejero et al., 2010).

In summary, our data show clearly that high P is related to poor outcome irrespective of other factors, and suggest that high daily FSH doses are associated with a high serum P, particularly if not balanced with appropriate LH activity. Nonetheless, large prospective and controlled studies are needed not only to better understand the underlying mechanisms but also we need studies to help guide patient management.

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Uterine transplantation: future directions

Sir,

We read with great interest the recent article by Wranning et al. (2010). The aim of their study was to explore the long-term function and fertility potential of an autotransplanted uterus within the context of a sheep model. This type of model was used because it compares well to the human uterus in terms of size and blood vessel anatomy and also, has a longer gestational period than a rodent model.

We commend the authors for their valuable and interesting assessment of whether surgery, ischaemia and neo-vasculature can affect the transplanted uterus. The study demonstrated for the first time that normal pregnancies can be achieved post-uterine autotransplantation in a large animal model. However, issues related to post-operative complications that precipitated the demise of 50% of the autotransplanted ewes are of interest.

We believe that our idea of using a large vessel (macrovascular) patch technique is likely to provide a higher transplant success rate. The idea is to harvest intact the internal iliac vessels and the uterine arterial and venous tree together with the uterus en bloc as a large vessel patch, as the evidence shows that the uterus resected en bloc is probably less likely to undergo vessel thrombosis. This was first demonstrated with limited success in a preserved human cadaver and freshly killed porcine and rabbit cadaveric models (Sieunarine et al., 2005). The technique was then applied to cross-transplant 20 rabbits (10 donors and 10 recipients) in two separate experiments. Assessments of the perfusion index and pulse oximetry on the uteri and post-mortem examinations were performed as per methods described by Moxey et al. (2006). In the first experiment, the six rabbit recipients survived the procedure of uterine cross-transplantation with satisfactory immediate post-operative recovery in all six of the allotransplants. After post-mortem and histological analyses in the short-term, all of the uteri appeared viable with no evidence of graft vessel thromboses. The complications experienced post-operatively were that three of six experienced paraplegia, two of six suffered from pulmonary embolus and one of six experienced secondary haemorrhage from the left horn of the uterine allograft (Sieunarine et al., 2008). The paraplegia occurred because of a
failure to adequately support the rabbit spine. Pulmonary emboli were a result of infusion under pressure of transplant medium and the secondary haemorrhage was caused by trimming of the graft after its harvesting, i.e. when it had no blood supply. All of these factors are therefore avoidable.

Our second experiment, most likely because of better understanding and greater experience in the necessary surgical techniques, revealed much better outcomes with all four rabbits surviving in the immediate post-operative period and two out of four during long-term follow-up (Hurst et al., 2009). These survival rates mirror the results reported by Wranning et al.

The team has now achieved successful uterine cross-transplantation in the rabbit model (Hurst et al., 2009). In addition, the large vessel patch technique has demonstrated its feasibility in humans with regards to anatomy. A team in New York, consisting of gynaec-oncology trained surgeons familiar with pelvic side wall dissection, has used the technique with success in harvesting uteri from local organ donor networks using existing protocols (Del Priore et al., 2007).

Furthermore, we respectfully highlight other important research areas that need to be explored (namely in the fields of immunology, fetal medicine and ethics) prior to making valid conclusions which relate to the human setting. They can be summarized by the following five questions:

(i) Is long-term graft survival possible following allogeneic uterine transplantation?
(ii) What are immunological mechanisms involved in uterine transplantation (rejection and tolerance patterns)?
(iii) What type of immunosuppression should be used?
(iv) Can pregnancy be established following allogeneic uterine transplantation and if so, are there any negative effects on the fetus/offspring?
(v) What psychological and ethical issues related to human transplantation need to be examined?

The process applied in exploring the above issues is the next significant leap in continuing to move uterine transplantation from the animal model into the human setting. It is important that a clear research protocol, agreed upon worldwide, is created and addresses not only the benefits of uterine transplantation but also the obvious drawbacks, with lucid strategies in tackling them.

We would again like to take this opportunity to congratulate the authors on their latest contribution to the jigsaw that, when complete, should lead to uterine transplantation in humans.

References


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