

## ABSTRACT

Wranning, Caiza A., 2007. **Surgery and ischemia in uterus transplantation - studies in various experimental models.** Department of Obstetrics and Gynecology, The Sahlgrenska Academy at Göteborg University, SE-413 45 Göteborg, Sweden.

The use of transplantation to enhance quality of life is a growing clinical field that also includes transplantation of reproductive organs. Transplantation of the uterus has been suggested as future method to treat uterus factor infertility. To investigate the feasibility of uterine transplantation and to develop safe methods, research must be performed in appropriate animal and *in vitro* models. This thesis investigates the effects of ischemia and reperfusion on functional, morphological and biochemical parameters in the uterus in several experimental models and also describes these models.

The tolerance of the uterus to cold ischemia was evaluated in a previously developed mouse model for uterus transplantation. Cold ischemia for 24 h did not impair the ability of the mouse uterus to implant embryos and produce normal offspring if University of Wisconsin preservation buffer (UW) was used during ischemia. Also, *in vitro* studies on human myometrium showed that myometrial contractions, protein synthesis and energy production were well preserved after cold ischemia in UW or the preservation solution Perfadex for 6 h.

A pig model for auto-transplantation of the uterus was developed and found to be of less value since the number of successful transplantations was low (21%) due to surgical difficulties related to the anatomy of the pig. In the development of a sheep model other surgical strategies could be used and the success rate was considerably higher (71%). Evaluation of biochemical and morphological parameters during reperfusion after of short time cold ischemia showed recovered metabolism and only a slight inflammatory response that was further reduced by the use of the preservation solution Perfadex during cold ischemia.

A rat model was also developed to complement to the mouse as a small animal model for uterine transplantation research. Morphological signs of post-ischemic inflammation in rat uteri transplanted after 24 h of cold ischemia were reduced by pre-treatment of the donor and the recipient with progesterone or prednisolone.

In summary, it was found that the mouse, the rat and the sheep can serve as appropriate model animals for studies of various aspects of uterus transplantation. It was also found that in these non-rejecting models the uterus is fairly resistant to injuries induced by surgery and cold ischemia and can tolerate cold ischemic storage for at least 24. However, in a possible future human application, organ injuries induced by ischemia should be reduced. Potential strategies to achieve this could include the use of short ischemic times, appropriate preservation solutions and anti-inflammatory pre-treatment of donor and recipient. These studies have moved the research front in uterine transplantation forward and it is predicted that uterine transplantation can reach the clinical setting within 5 years.

**Key words:** animal models, cold ischemia-reperfusion injury, inflammation, transplantation, uterus

# **SURGERY AND ISCHEMIA IN UTERUS TRANSPLANTATION: studies in various experimental models**

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Avhandlingen baseras på följande arbeten:

- I. Pregnancy in transplanted mouse uterus after long-term cold ischaemic preservation.**  
Racho El-Akouri R., Wranning C.A., Mölne J., Kurlberg G., Brännström M.  
*Human Reproduction*. 2003 Oct;18(10):2024-30.
- II. Short-term ischaemic storage of human uterine myometrium--basic studies towards uterine transplantation.**  
Wranning C.A., Mölne J. El-Akouri R.R., Kurlberg G., Brännström M.  
*Human Reproduction*. 2005 Oct;20(10):2736-44.
- III. Auto-transplantation of the uterus in the domestic pig (*Sus scrofa*): Surgical technique and early reperfusion events.**  
Wranning C.A., El-Akouri R.R., Lundmark C., Dahm-Kähler P., Mölne J., Enskog A., Brännström M.  
*Journal of Obstetrics and Gynaecology Research* 2006 Aug;32(4):358-67.
- IV. Transplantation of the uterus in the sheep – oxidative stress and reperfusion injury after short time cold storage.**  
Wranning C.A., Dahm-Kähler P., Mölne J., Nilsson U.A., Enskog A., Brännström M.  
*Fertility and Sterility* 2007. *In press*
- V. Effects of progesterone and prednisolone on post-operative inflammation after cold ischemia in a rat model for uterus transplantation.**  
Wranning C.A., Mölne J., Kurlberg G., Brännström M.  
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