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Uterus transplantation: an experimental study in the rat model

Akademisk avhandling

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av

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This thesis is based on the following papers:

I. Uterus transplantation in the rat: model development, surgical learning and morphological evaluation of healing.
Wranning CA, Akhi SN, Kurlberg G, Brännström M.
Acta Obstet Gynecol Scand. 2008;87:1239-47.

II. Pregnancy after syngeneic uterus transplantation and spontaneous mating in the rat.
Wranning CA, Akhi SN, Díaz-García C, Brännström M.
Hum Reprod. 2011;26:553-8.

III. Uterine rejection after allogeneic uterus transplantation in the rat is effectively suppressed by tacrolimus.
Akhi SN, Díaz-García C, El-Akouri RR, Wranning CA, Mölne J, Brännström M.
Fertil Steril 2013; in press.

IV. Monitoring rejection after uterus transplantation: morphological assessment of different sites of a uterine allograft in a rat model.
Akhi SN, Díaz-García C, El-Akouri RR, Brännström M, Mölne J.
In manuscript.

V. First report on fertility after allogeneic uterus transplantation.
Díaz-García C, Akhi SN, Wallin A, Pellicer A, Brännström M.
Acta Obstet Gynecol Scand. 2010;89:1491-4.

VI. Live offspring after allogeneic uterus transplantation in the rat.
Akhi SN, Díaz-García C, Brännström M.
In manuscript.

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ABSTRACT

Uterus transplantation: an experimental study in the rat model

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One of the last frontiers to conquer in infertility research is to find a treatment for uterine factor infertility, which affects around 2500 Swedish women. These women cannot become pregnant or carry a pregnancy due to absence of uterus or presence of non-functioning uterus. During recent years, several animal models have been used in research to develop uterus transplantation into a clinical treatment for uterine factor infertility. In the present study, the rat was used as a uterus transplantation model to look at various aspects of the procedure.

A first model for uterus transplantation in the rat, with vascular anastomosis, was developed. In this model, the native uterus was compared to a heterotopically placed grafted uterus within the same strain of inbred rats. There was good viability of the tissue and an untrained surgeon could master the procedure after around 20-30 surgeries.
In the second study, the uterus transplantation model was modified further to allow for spontaneous mating and test of pregnancy. Pregnancy was achieved after natural mating and the number of pups and growth trajectory of the pups in this model was similar to that of controls.
In tests of allogeneic uterus transplantation, effects of immunosuppression were evaluated. Transplanted rats received either no treatment or tacrolimus as monotherapy. One sham-surgery group and one sham-group treated with tacrolimus were included as controls. It was shown that rejection occurred in the non-tacrolimus treated transplanted group but that normal uterine morphology was seen in the tacrolimus treated transplanted group. Low numbers of T-cells were seen in most allografts treated with tacrolimus. Levels of the cytokines IL-1 and IP-10 were increased in the non-treated transplanted group and levels of the implantation marker galectin-1 were normalized after tacrolimus treatment.
Different sites of diagnosis of rejection were tested. In a fully allogeneic model, the histology of the graft was analysed at day 4 or 7. On day 4, morphological signs of early rejection were found both in the myometrium, endometrium, uterine cervix and in the blood vessels. Inflammation with primarily neutrophils and lymphocytes was seen. At day 7, the inflammation was greater with also focal hemorrhage. It can be concluded that early events of rejection in a uterus transplantation model is seen in all the examined compartments and the cervix may be an appropriate site for clinical diagnosis of early rejection.
The most important functional issue to test in uterus transplantation is whether uterine allografts can carry a pregnancy. Rats with allogeneic uterine transplants were treated with tacrolimus. The pregnancy rate was similar in the transplanted and tacrolimus-treated group as in the control groups. These experiments ended during late gestation and no further follow-up of the pregnancy was performed.
In a follow-up paper of allogeneic transplantation, the pregnancies went to term. Birth weight was similar in the transplanted group that was treated with tacrolimus as in the control groups. The post-natal growth up to 100 days was also similar, but with somewhat larger weight for males born from the uterus transplanted group.

In summary, the thesis presents important background data for further development of uterus transplantation towards clinical introduction.

Keywords: infertility, microsurgery, pregnancy, rat, transplantation, uterus

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