

Rejection and Immunosuppression at Uterus Transplantation: an experimental study in rodents

Klaus Groth

Department of Obstetrics and Gynecology, Institute of Clinical Sciences, Sahlgrenska Academy,
University of Gothenburg, Sweden, 2009

Uterus transplantation is developed as a possible treatment for patients with absolute uterine factor infertility. There has been one attempt to transplant a human uterus, which however failed and more basic research is needed before another attempt is performed. The aim of the thesis was to describe the rejection process after uterus transplantation in rodent models and to study the effects of the most widely used immunosuppressant, cyclosporine A (CsA) on this process. The effect of CsA on fertility was also studied in exposed mice and their offspring.

In a fully allogenic mouse model microscopic signs of rejection were found from day five. Blood flow was lower as compared to the native uterus. The gross morphological signs of rejections were initial swelling of the transplant and later the transplant became firmer in texture with a clear color change. There was an early infiltration of macrophages into the myometrium of the graft from day 2 and in the endometrium at day 5. Density of CD8⁺ cytotoxic T-cells increased in the graft from day 5 but there was only a transient increase in CD4⁺ T-helper cells. In a semi-allogenic mouse model different doses of CsA were tested. In the non-treated transplanted animals pronounced inflammation was seen. In the CsA treated groups inflammation was less pronounced. The tissue density of CD8⁺ cytotoxic T-cells was higher in treated group. Similar microscopic findings of rejection were also present in an allogenic model in the rat where CsA was used. It was found that mRNA levels of interleukin-1 α were decreased and the levels of galectin-1 mRNA were increased in the CsA group. The study on CsA:s effect on reproduction, in two generations showed that high doses of CsA reduced implantation rates/fetal survival and did also reduce adolescent growth in offspring but not fertility. Reduced fetal weight was seen in offspring of female exposed to CsA in utero.

The collective result from these studies form a base for future studies of rejection of uterus transplants and of studies aiming to optimise immunosuppression to inhibit rejection and minimise the negative effects of immunosuppression on fertility, pregnancy and future health of offspring.

Key words: *cyclosporine A, fertility, mouse, pregnancy, rat, rejection, transplantation, uterus*

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Klaus Groth
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- I. Rejection patterns in allogeneic uterus transplantation in the mouse.
El-Akouri RR, Mölne J, Groth K, Kurlberg G, Brännström M.
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- II. Rejection of the transplanted uterus is suppressed by cyclosporine A in semi-allogeneic mouse model. a
Wranning CA, El-Akouri RR, Groth K, Mölne J, Parra AK, Brännström M.
Hum Reprod 2007;22:372-379.
- III. Rejection of allogeneic uterus transplant in the mouse – time-dependent and site-specific infiltration of leukocyte subtypes.
Groth K, El-Akouri R, Wranning CA, Mölne J, Brännström M.
Hum Reprod 2009;24:2746-54.
- IV. Cyclosporine A exposure during pregnancy in mice: effects on reproductive performance in mothers and offspring.
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Fakultetsopponent Handledare

Professor Mohamed Aboulghar Professor Mats Brännström
Cairo University and *Biträdande handledare*
the Egyptian IVF-ET Centre, Caiza Almén-Wranning, Med. Dr
Maadi, Institutionen för kliniska vetenskaper
Egypten Sahlgrenska akademien vid Göteborgs universitet