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Adenoviral Gene Therapy and Fertility

Distribution Studies in Reproductive Organs and Risk of Vertical Transmission in Female Rabbits and Rats

Doctoral dissertation

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ABSTRACT

Gene medicines are modern tools for treating a wide variety of diseases in all age groups, including patients with reproductive capability. As the action of gene medicines is directed at the genome itself, the safety criteria of these drugs exceed those of conventional medicines. Our aim was to study the distribution of clinical grade adenoviral transfer gene vectors in the female reproductive tract and their effects on fertility and offspring. Gene vectors were administered into the fetal exocoelomic cavity in rats and into uterine lumen in rabbits, and intravascularly into uterine and ovarian arteries in rabbits using microsurgical and angiographical operative methods. A LacZ marker gene and a suicide gene, thymidine kinase, were used as transgenes. Baculoviruses and plasmid/liposomes were used to compare the effects between the vectors.

The materno-fetal leakage of the adenoviral vector seems to be prevented by the fetal membranes, but transplacental escape of the gene vector may occur. After administration of adenoviruses into the fetal exocoelomic cavity of rats the vector was blocked by a rodent fetal membrane. In addition, intraluminal vector administration into pregnant rabbits did not affect the fetuses. After intravascular gene transfer the transgene DNA was observed in the liver samples of the offspring in subsequent matings, but the number of positive young declined over time. Neither signs of vertical transmission nor gene expression in fetal organs were noted.

All ovarian and uterine tissues could be transduced with adenoviral vectors and the transduction pattern varied with the administration route and stage of the reproductive cycle. After intraluminal uterine gene transfer the transgene leaked into the endometrial stroma and uterine muscular wall during the inactive stage. However, during the proliferative stage the transduction was restricted to the dividing endometrial epithelial cells. Shortly after intravascular administration of adenoviruses into pregnant rabbits a moderate transfection rate was noted in the follicular cells and in the cells of the corpus luteum, in addition to a low expression rate in the primordial oocytes in the ovaries. With thymidine kinase suicide gene therapy morphological changes were observed in oocytes in histological stainings, but in long-term follow-up no effect on fertility was observed and normal progeny were born from subsequent matings of the treated rabbits. In non-pregnant rabbits the intravascular gene transfer did not affect the oocytes, and transgene expression was restricted to the thecal and stromal cells. With baculoviruses and plasmid/liposomes no transfection was noted in ovaries and uteri, in spite of a relatively high transfection rate in primordial oocytes in pregnant rabbits with plasmid/liposomes.

We conclude that the safety of adenoviral gene therapy in female reproductive organs is good, because the exposure of rabbit and rat ovaries and uteri to adenoviral gene therapy did not affect fertility or the germ line in long-term follow-up, despite high transduction efficiency in uterine and ovarian cells being observed shortly after the gene transfer. However, the leakage of the transgene into the offspring could not be excluded after large dose exposure via the circulation, although no integration of the transgene into the genome was detected.

National Library of Medicine Classification: QZ 52, QU 470, QU 475, QZ 42, WP 565, WP 320
Medical Subject Headings: Gene Therapy/adverse effects; Genetic Vectors/adverse effects; Safety; Fertility; Germ Cells, Ovary; Oocytes; Uterus; Adenoviridae; Baculoviridae; Plasmids; Transgenes; Rabbits; Rats.

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