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Title and English abstract

Title: Glycodelin and Differentiation in Endometrium and Ovary: Clinical Aspects Related to Reproduction and Epithelial Ovarian Cancer

Abstract: Glycodelin is the major progesterone-regulated lipocalin protein of the reproductive axis. It has contraceptive and immunomodulatory functions, and it may play an important role in differentiation and glandular morphogenesis. The aim of this study was to investigate the expression of glycodelin in three clinical settings: in the fertile window, in the window of implantation, and in ovarian serous carcinoma, with special attention to changes in tissue differentiation.

Glycodelin is a uterine secretory glycoprotein that inhibits sperm-egg binding, and is not normally secreted during the fertile window at midcycle. This phase of the menstrual cycle was specifically addressed in respect to induced secretion of contraceptive glycodelin. Evidence showed that a levonorgestrel-releasing IUD is accompanied by inappropriate expression of glycodelin in endometrium between days 7 and 16 of the menstrual cycle (6 of 6 cases). The same was also found in copper-IUD-wearing women, but less frequently (4 of 11 cases, $P < 0.0345$). Experiments employing in situ hybridization localized glycodelin mRNA into endometrial glands in the midcycle endometrium, confirming the cellular site of synthesis.

Another group of contraceptive users, in whom uterine glycodelin secretion was studied during the fertile window, were levonorgestrel subdermal implant-wearing women. Of the endometrial specimens from these women, 80% stained positive for glycodelin. The endometrial morphology of these women showed proliferative (71%), inactive/weakly proliferative (19%), menstrual or regenerating (6.5%), and other patterns (2.8%). Of these, 79%, 71%, 100%, and 100% were glycodelin-positive. During the midcycle, when glycodelin is not normally expressed, of 19 cases 89% showed glycodelin expression.

Another point of interest is the window of implantation that in a normal menstrual cycle spans from LH+4/5 to LH+10. Factors affecting glycodelin expression during the phase of uterine receptivity were chosen in view of the immunosuppressive properties of glycodelin and its putative role in feto-maternal defense mechanisms. In women with COH (controlled ovarian hyperstimulation), endometrium is exposed to high concentrations of ovarian steroids and other substances. In such women, the proportion of glycodelin-positive endometrial cells was elevated above values in normal controls. This was evident throughout the window of implantation. Glycodelin was present in the endometrial glands, but not in the stroma or surface epithelium. A positive correlation appeared between glycodelin expression and serum estradiol levels ($r = 0.5$, $P < 0.001$) in normal menstrual cycles, and glycodelin and advanced histology in COH cycles ($r = 0.63$, $P = 0.01$). Neither LH nor progesterone serum levels were correlated with endometrial glycodelin expression.

Because ethical constraints limit studies on endometrium during the peri-implantation phase of a fertile cycle, the donor oocyte model was chosen for investigation of candidate endometrial markers in respect to uterine receptivity. Endometrial biopsies from cycle days 21 to 23 of oocyte recipients undergoing mock hormonal treatment cycles were evaluated by standard histological criteria and by immunohistochemical staining for glycodelin and $\alpha v \beta 3$ integrin. Oocyte recipients underwent identical hormonal replacement

protocols for both the mock treatment cycle and the actual oocyte donation cycle. Endometrial histology of these women showed 62 (61.3%) in-phase, 34 (33.7%) dyssynchronous, 2 (2.0%) immature, and 3 (3.0%) advanced maturation. The clinical outcomes of patients with either in-phase or dyssynchronous endometria were similar. Strong correlations existed between endometrial glandular dating and either glycodeilin- or $\alpha v \beta 3$ integrin-immunostaining intensity ($P < 0.001$ for both). Glycodeilin and $\alpha v \beta 3$ integrin immunostaining intensities were also highly correlated with each other ($P < 0.001$).

In ovarian serous carcinomas from 460 patients, we determined glycodeilin expression by immunohistochemistry of tissue microarrays, and analyzed the results in relation to the progesterone receptors PRA (progesterone receptor subtype A) and PRB (progesterone receptor subtype B), to clinical parameters, and to survival. Glycodeilin was localized in the cytoplasm of tumor cells, whereas vascular endothelium in tumor tissue was glycodeilin-negative. Glycodeilin expression was more frequent in well-differentiated (grade I, 79%) than in poorly differentiated carcinomas (grade III, 51%, $P < 0.0001$), and also more frequent in early than in advanced stage carcinomas ($P = 0.002$). Cytoplasmic glycodeilin was often co-expressed with nuclear PRA and PRB. Whereas this was not consistent in all tumors, a positive correlation existed in the tumor between the presence of glycodeilin and progesterone receptors ($P < 0.02$), but not between the presence or absence of glycodeilin in the tumor and the CA-125serum concentration. Although in multivariate analysis glycodeilin was not an independent variable, those patients with glycodeilin-expressing tumors showed a higher 5-year overall survival than did those whose tumors were glycodeilin-negative (55% vs. 39%, $P < 0.0001$, hazard ratio in univariate analysis 0.57, CI 0.44-0.74). In the patients with grade I tumors or stage III disease, this difference was pronounced. In the latter group, the 10-year survival probability of those with glycodeilin-positive tumors was more than twice as high as that of those with glycodeilin-negative tumors. This also occurred within well-defined clinical categories, e.g., in stage III/grade II and stage III/grade III carcinomas, in which patients with glycodeilin-positive tumors exhibited a significantly better 10-year overall survival than did those with glycodeilin-negative tumors.

Based on the potent inhibitory activity of glycodeilin on sperm-egg binding and secretion into uterine fluid, in IUD and subdermal-implant-wearing women, glycodeilin secretion during the otherwise fertile window may thus lead, before fertilization, to exposure of sperm to contraceptive glycodeilin. This may contribute to the effectiveness of such contraceptive devices. Studies of the window of implantation showed oocyte donors undergoing COH treatment to have significantly higher endometrial glycodeilin expression throughout the implantation window than did women with natural cycles. Endometrial glycodeilin expression frequently occurred in progesterone/estrogen-stimulated mock cycles. In ovarian serous carcinoma, glycodeilin expression is related to differentiation and offers a better prognosis.

The date of disputation

October 5, 2003

A possible link to the full text

<http://ethesis.helsinki.fi>