# CYCLOOXYGENASE-2 IN MYOMETRIUM DURING PARTURITION AND IN OVARIAN CARCINOMA


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Academic Dissertation

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**Cyclooxygenase-2 in myometrium during parturition and in ovarian carcinoma**

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Prostanoids (prostaglandins, prostacyclin, and thromboxane) play an important role in several physiological and pathological processes in the female reproductive organs. Cyclooxygenase (COX) enzymes are the rate-limiting enzymes in the conversion of arachidonic acid to prostanoids. COX-2, the inducible COX isoenzyme, is expressed at low levels in basal conditions, but is induced by cytokines, tumor promoters, and hormones. The aim of this study was to investigate COX-2 expression in gynecological organs during parturition and in ovarian carcinoma.

We investigated the expression of COX-2 in myometrial samples during parturition by Northern blot analysis, and observed a 15-fold elevation in COX-2 mRNA expression at the onset of labor. Cultured human myometrial cells expressed low levels of COX-2 mRNA in baseline condition, but stimulation of these cells with a proinflammatory cytokine interleukin-1β caused an induction of COX-2 mRNA and active COX-2 protein expression. These data suggest that COX-2 is an important inducible prostanoid-producing enzyme in the myometrium during parturition. However, although selective COX-2 inhibitors may be effective in prevention of premature birth, their use is limited by fetal side-effects, such as oligohydramnions and constriction or premature closure of the fetal ductus arteriosus.

In order to investigate the role of COX-2 in gynecological malignancies, the most lethal gynecological carcinoma, ovarian carcinoma, was studied. COX-2 protein expression was investigated by immunohistochemistry in 442 serous and 56 mucinous ovarian carcinoma specimens. COX-2 immunoreactivity localized mainly to the epithelial cancer cells, but also

in the stromal compartment of the tumor, especially in the mucinous carcinomas. COX-2 expression was elevated in the epithelial cancer cells more often in the serous (70%) than in the mucinous (39%) tumors ($P<0.0001$). Elevated epithelial expression of COX-2 associated with high histological grade in both histologies and with reduced survival in serous carcinoma. Furthermore, cytoplasmic expression of the mRNA stability factor HuR correlated with epithelial COX-2 expression in both histologies, and was associated with reduced survival in serous ovarian tumors. Thus, HuR is the first mRNA stability protein, the expression of which has been linked to reduced survival in carcinoma patients.