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Relaxin and the control of primate parturition

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Summary

In primate pregnancy, circulating relaxin, solely a product of the corpus luteum, peaks in the first trimester of pregnancy then declines and levels off for the remainder of pregnancy. Relaxin actions in pregnancy include increasing cervical pro-MMP-1 and pro-MMP-3 and decreasing TIMP-1, changes which soften the cervix. Relaxin, from early pregnancy, increases endometrial natural killer cells, macrophages and neutrophils, blood flow and arterial number. Hyperrelaxinemia correlates with preterm birth.

Key words

Relaxin, Primate, Pregnancy, Parturition

In women, relaxin is produced by the corpus luteum, decidua and placenta. HCG is the stimulus to luteal relaxin secretion. hCG must be timed to the 8-10th day of luteal life. Relaxin secretion does not occur if hCG is given on day 4-5 of the luteal phase. There is no relaxin secretion in egg donation pregnancies, which have no corpus luteum. Levels of circulating relaxin are regulated by the number of fetuses (hCG levels) and the method of ovulation induction (luteal mass). Luteal mass is the more important determinant. A second fetus causes a 1.4-fold increase in circulating relaxin. Ovulation induction with FSH causes an additional 3.3-fold increase in circulating relaxin. Ovarian stimulation prior to IVF is associated with a 2-fold increase in the incidence of preterm birth.

We measured serum relaxin in women with spontaneous (control) and ovulation induction (study group) pregnancies at 6-12 weeks of pregnancy and determined the outcomes. The mean of the first trimester relaxin levels (6-12 weeks) in controls was 1.18 ng/ml. 3SD above the mean was 3.25 ng/ml, our definition of hyperrelaxinemia. A logistic regression model showed that a 5 ng/ml increase in relaxin increases the odds ratio of prematurity by 2.06, ($p<0.013$). The elevated relaxin levels in ovulation induction pregnancies persisted throughout pregnancy.

Dilation and ripening of the human cervix involves various factors which cause rearrangement of cervical connective tissue and leukocyte infiltration. Using an in vitro cervical lower uterine segment model with tissue obtained at delivery (LUS), ^{125}I-relaxin bound to human lower uterine segment fibroblasts was displaced by increasing levels of relaxin. Scatchard analysis of relaxin binding demonstrated the

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Kd was 4.36 ± 1.7 x 10^{-9}M. Using the LUS model, we showed that relaxin stimulates expression of procollagenase (pro-MMP-1) protein/mRNA, progelatinase (pro-MMP-2) protein/mRNA, prostromelysin (pro-MMP-3) protein/mRNA and inhibits expression of TIMP-1 protein/mRNA. Thus relaxin is a positive regulator of matrix metalloproteinases at the level of the cervix, the net effect of which is increased collagenase activity. Relaxin also stimulates interleukin-8 in human LUS, increasing the influx of leukocytes.

An in vivo model of early pregnancy using ovariectomized rhesus monkeys was developed by administering estradiol implants, progesterone implants and relaxin injections to produce patterns and levels mimicking early pregnancy. Controls were identical except for being given vehicle instead of relaxin. Hysterectomies were performed on simulated day 42 of pregnancy. Relaxin signficiantly increased uterine weight but not body weight. Relaxin decreased cervical collagen and disrupted the organized structure of the cervix. Relaxin increased cervical pro-MMP-7, an invasion cytokine implicated in implantation. Relaxin decreased cervical lumican, a substance needed to hold the extracellular matrix together. Cervical elastin was decreased by relaxin which disrupted elastin fibers. All these changes suggest that relaxin regulates changes which occur in the cervix starting in early pregnancy.

Elevation of relaxin by a 24 hour infusion in women at term, producing 30-fold increased levels over baseline at 41 weeks of pregnancy, did not increase cervical dilation, shorten the time to delivery, the incidence of spontaneous labor or shorten the time to active labor. Relaxin infusion decreased BUN and creatinine, but did not affect timing of delivery acutely. Perhaps relaxin takes more time to affect structural changes in connective tissue.