LOSS OF INHIBIN NEGATIVE FEEDBACK IN THE PITUITARY LEADS TO ENHANCED OVULATION BUT PREGNANCY FAILURE IN MICE

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Follicle-stimulating hormone (FSH) is an essential regulator of female gonadal function. Inhibins are TGFβ family ligands that suppress FSH synthesis by pituitary gonadotrope cells. Inhibins require a co-receptor, betaglycan or TGFBR3L, to mediate their actions. Female mice with a gonadotrope-specific deletion of betaglycan or global deletion of *Tgfbr3l* exhibit enhanced follicle growth and produce larger litters compared to controls. Females with both co-receptors knocked out (hereafter dKO) show marked increases in serum FSH levels, ovulate 3-4 times as many eggs in natural cycles compared to controls, but are infertile. dKO females become pregnant and show an increased number of implanted embryos at 7.5 days post coitum (dpc). Nevertheless, by 10.5 dpc, their embryos are dead or dying. Wild-type surrogates give birth to live young following transplantation of embryos from dKO females. Conversely, pseudopregnant control but not dKO females carry transferred wild-type embryos to term. Thus, the maternal environment in dKO mice cannot support full-term pregnancies. We suspected a deleterious effect of elevated estrogens. Consistent with this idea, treatment with the aromatase inhibitor anastrozole increased embryo survival in dKO mice. We are currently characterizing the maternal hormonal environment throughout gestation and investigating placental structure/function to gain more insight into the precise nature and cause of pregnancy failure in dKO mice. Collectively, the data indicate that ovarian overstimulation, due to the loss of inhibin negative feedback, is compatible with enhanced ovulation but not fertility.