Maternal Tamoxifen Effects on Mouse Pregnancy and Placental Development

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A significant reduction in pregnancy rates is observed among reproductive age female cancer survivors treated with tamoxifen (TAM). Tamoxifen is a selective estrogen receptor modulator (SERM) used to treat estrogen-sensitive (ER+) breast cancer. While it has protective estrogen receptor inhibitory effects in breast tissue, it is an agonist in uterine tissue. We have used a mouse model to examine the effects of TAM on implantation and the placenta after exposure. There were two primary cohorts of CF1 female mice – age-matched control (n=27) and a TAM-treated group (n-54). Mature female mice received a diet of regular chow (control) or chow supplemented with 250 mg of TAM per Kg of chow for 3 weeks, then TAM treatment ended, all mice were fed control diet, and mice were housed for 1-4 weeks washout prior to being mated with fertile B6D2F1 males. The pregnancy rate of the control group was 67% and 26.3% for the treated group. The average number of pups was 13.2 per litter and 4.9 per litter for the control and treated group, respectively. Tamoxifen treated females had significantly lower pregnancy rates, even after extended wash-out: 7.7%, 13.3%, 26.3%, 28.6% (0, 1, 2, 3wks wash-out) compared to controls 67%. Time to conception was longer for TAM females, 4, 2, 3, 4wks vs 0wks for controls. Placentas were collected at E16 of development, fixed, and embedded in paraffin, sectioned using a microtome, scanned, and analyzed after conducting immunohistochemistry (IHC) or Hematoxylin and Eosin (H&E) staining. Images were scanned for positive staining of the antibodies CD31 (endothelial cells), TPBPA, GLUT1 (glucose transporter), and P57. Uteri with implantation resorption sites were found only in the treated group of mice. GLUT1 was ubiquitously stained throughout the entire placenta. Using the antibody TPBPA as a marker for the junctional zone spongiotrophoblasts, and H&E staining, we were able to obtain the average surface area measurements of the primary layers of the fetal placenta; the labyrinth and junctional zone (JZ). In the control group, the fetal placenta was made up of 59.4% labyrinth and 40.6% JZ. In the TAM treated group, the fetal placenta was made up of 45.3% labyrinth and 54.7% JZ, with spongiotrophoblast cells of the JZ growing in a disordered fashion into the labyrinth zone. Quantification of P57 expression in the labyrinth zone of the placenta revealed a significant decrease in p57 expressing trophoblast cells in the labyrinth zone of TAM treated mice. In addition, CD31 quantification showed a significant increase in CD31 immunoreactivity in the labyrinth zone of the TAM treated mice. Along with the reduced P57 in the trophoblast cells in the labyrinth zone, this suggests reduced numbers of trophoblast cells in the labyrinth zone of TAM treated mouse placentas. These results suggest potential long-term effects of tamoxifen on the placenta and pregnancy, even after an extended wash-out period.

Keywords: Tamoxifen, pregnancy rates, placenta and implantation

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