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Gene-Environment Interactions in Transplacental Ovarian Toxicity and Tumorigenesis. Luderer U. University of California Irvine, Irvine, CA, United States.

Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous environmental pollutants found in tobacco smoke, air pollution, and grilled foods. Women who smoke have earlier menopause and increased risk of ovarian cancer, and this may be related to PAH exposure. Prenatal exposure to PAHs causes premature reproductive senescence in mice. Reactive metabolites and reactive oxygen species generated during PAH metabolism are detoxified by reactions involving glutathione (GSH). We hypothesized that embryonic mice with GSH deficiency, due to deletion of the modifier subunit of glutamate cysteine ligase (*Gclm*), the rate-limiting enzyme in GSH synthesis, have increased destruction of oogonia and ovarian tumorigenesis after transplacental exposure to the PAH benzo[a]pyrene (BaP) compared to *Gclm*+/+ females. *Gclm*+/- females and males were mated, and dams were treated with 0, 2, or 10mg/kg/day BaP by gavage from 6.5–15.5 days postcoitum. Compared to vehicle-treated female offspring of the same genotype, *Gclm*-/- BaP-treated females had significantly greater decrements in fertility than *Gclm*+/+ BaP-treated females. No follicles remained in ovaries of 7.5 month old *Gclm*-/- or *Gclm*+/+ mice exposed to 10mg/kg BaP prenatally. Follicle numbers were decreased in 2mg/kg BaP-treated mice, with greater relative decreases in the *Gclm*-/- than the *Gclm*+/+ females. Both *Gclm*-/- and *Gclm*+/+ BaP-treated females developed ovarian tumors in a dose-related manner, but tumors were more prevalent in *Gclm*-/- females. These results demonstrate that prenatal exposure to BaP causes premature ovarian failure and ovarian tumors and that embryonic GSH deficiency increases sensitivity to these transplacental effects of BaP. Ongoing studies are investigating the mechanisms involved.