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| **Fetal drug exposure after maternally administered CFTR modulators Elexacaftor/Tezacaftor/Ivacaftor in a rat model** |
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| **Background:** The potential effects of the very effective cystic fibrosis triple combination drug, Elexacaftor/Tezacaftor/Ivacaftor (ETI) in pregnancy on prenatal development of offspring remain largely unknown. We aimed to investigate the fetal tissue distribution pattern of maternally administered ETI by placental transfer in the rat fetuses.  **Study Design and Methods**: Sprague Dawley pregnant rats were administered ETI (6.7 mg/kg/d elexacaftor + 3.5 mg/kg/d tezacaftor + 25 mg/kg/d ivacaftor) traced with [3H]-ivacaftor in single dose acute experiments (intraperitoneal injection) or treated orally with ETI (the same dose) for 7 days in sub-chronic experiments. Fetal tissue samples were collected at embryonic day (E) 19 and analyzed using liquid scintillation counting for acute experiments or liquid chromatography-mass spectrometry for sub-chronic experiments.  **Results:** On day E19, after acute exposure, the entry of ivacaftor into fetal brain (brain/plasma concentration ratios <50%) was significantly lower than to other tissues (>100%).  However, after sub-chronic exposure, the entry of all 3 components into the developing brain was comparably extensive as into other tissues (tissue/plasma ratios, 260 – 1000%). Each component of ETI accumulated in different fetal tissues to approximately equal extent. Inter-litter differences on fetal drug distribution were found in cortex for ivacaftor, muscle for tezacaftor and cortex and mid/hindbrain for elexacaftor. Fetal plasma concentrations of ETI (ng/mL) were variable between litters. The entry of ivacaftor and tezacaftor into adult brain appeared to be restricted (<100%).  **Conclusion:** Fetal rats are exposed to maternally ingested ETI after sub-chronic exposure, potentially impacting fetal development. The brain entry data highlights the need for attention be paid to any long-term potential effects ETI exposure could have on normal brain development.  **Grant Support:**  EKS-F is supported by the National Health and Medical Research Council (Grant ID: APP1157287) Cystic Fibrosis Australia (Innovation Award 2021) and the University of Melbourne. |