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| **Late pregnancy Elexacaftor/Tezacaftor/Ivacaftor exposure may harm developing thymus and cortex** |
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| **Introduction/Aim:** The highly effective CFTR modulator therapy Elexacaftor/Tezacaftor/Ivacaftor (ETI) has increased the quality of life and fertility of people with cystic fibrosis (CF). However, the risks it might pose if taken during pregnancy remain largely unknown. This study aimed to assess the safety of ETI on fetal structural development and genetic changes.**Methods:** Pregnant Sprague Dawley rats were fed orally with ETI (6.7 mg/kg/d Elexacaftor + 3.5 mg/kg/d Tezacaftor + 25 mg/kg/d Ivacaftor) from embryonic day (E) 12 to E19 and multiple fetal tissues were collected at E19. By comparing with control groups, tissues from ETI-treated groups were assessed for structural changes through histology hematoxilin & eosin (H&E) and Alcian blue periodic acid Schiff (AB/PAS) staining, and for genetic changes using next generation RNA sequencing.**Results:** No overt structural abnormalities and very few differentially expressed genes (DEG) were detected in fetal liver (2 DEG), lung (4 DEG) and small intestine (5 DEG) after 7-day ETI exposure. A total of 29 DEG (27 upregulated and 2 downregulated) were identified in fetal thymus, most of which were functionally linked and related to striated muscle (myosin) development. In fetal cortex, a total of 44 downregulated and 4 upregulated genes were identified and a group of these were involved in neurogenesis, neuronal differentiation and central nervous system development.**Conclusion:** Sub-chronic exposure to ETI during late pregnancy does not appear to pose a significant risk to structural and genetic development of fetal liver, lung and small intestine. In contrast, ETI exposure may indue fetal thymic myoid cell expansion and have effects on cortical development, which needs to be investigated further in follow-up studies. **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. |