Investigation into the effects of Sodium Valproate on Developing Fetal Gonads in Vitro

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One in every 200 pregnant women suffer from epilepsy, requiring treatment with anti-epileptic drugs (AEDs) which prevent seizures that can cause harm to the mother and fetus. Sodium valproate (SV) is an AED that was contraindicated in women of childbearing age in 2018 due to its significant teratogenic risks and in January 2024, The Medicines and Healthcare products Regulatory Agency (MHRA) issued a national patient safety alert advising that SV prescriptions for all patients under 55 will be required to be signed off by two independent specialists. Prior to 2018, SV was prescribed during pregnancy and around 20,000 children in the UK are estimated to have been prenatally exposed to SV. Approximately 40% of these children are at risk of developmental disorders, yet the assessment of its effects on the developing fetal gonads has been limited. We have investigated this using tissue culture of mouse fetal gonads. Mouse gonads were collected from embryonic day 13.5 (E13.5) CD1 embryos. Fetal ovaries were cultured for 12 days, with either DMSO or 10 µg/ml of SV added to the culture media for the first 6 days of culture only (n=6). Ovarian follicle number and health were analysed histologically, and levels of DNA double-strand breaks (DSBs) were examined by carrying out immunohistochemistry for yH2AX. Fetal testes were cultured for 96 hours with either DMSO or 10 µg/ml of SV for the whole duration of culture (n=5). ELISA was used to assess testosterone concentrations in culture media collected at 48 and 96 hours. Gross morphology of testicular tissue was examined histologically. SV treatment did not significantly impact the number or health of follicles in cultured ovaries, and did not impact the level of DSBs. Furthermore, testicular tissue health and seminiferous cord definition were not impacted by SV exposure. However, testosterone levels were significantly decreased between 48 and 96 hours of culture in SV treated testes ($p < 0.01$). Overall, our results suggest that exposure to clinically relevant doses of SV does not have a detrimental impact on the morphology of the developing fetal ovary or testis. However, SV does negatively impact testosterone secretion, suggesting a potential impact on the fetal Leydig cells. Further studies are needed to confirm these findings and to determine whether similar effects are observed in vivo and/or in human fetal gonads.