A human placental villous explant model to study the toxicity of drugs

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Interference of drugs with placental function may contribute to adverse pregnancy outcomes. To better understand the toxicological potential of drugs on the human placenta, we set up a human placental villous explant model and studied the effect of several tyrosine kinase inhibitors and known cytotoxic agents used during pregnancy.

Samples of placental villous tissue were excised within 60 minutes after delivery and cultured at 37°C, 5% CO_2. Incubation with drugs was performed from day 3 of culture onwards. Effects of crizotinib, sunitinib, imatinib, doxorubicin, carboplatin, placlitaxel, cisplatin and tofacitinib were measured after 72 hours of incubation. Viability was assessed via MTT and LDH assays. Progesterone and estrone secretion into the culture medium were measured via LC-MS/MS.

Explants demonstrated stable LDH excretion between day 3 (2.6±0.7 mIU/mg wet weight/24h) and 7 (2.0±0.4 mIU/mg wet weight/24h), confirming tissue viability. This was in line with the results from MTT assays. Estrone and progesterone excretion was also observed, but levels fluctuated over time. Test compounds reduced explant viability with different potencies. Doxorubicin was the most potent inhibitor, reducing viability by 65±14%, already at 10 µM. In contrast, paclitaxel and carboplatin did not significantly affect viability up to concentrations of 100 µM. Reductions in cell viability appeared to be paralleled by a decrease in progesterone excretion into the medium.

In conclusion, we found that it is feasible to establish cultures of placental villous explants and measure adverse effects of drugs in this system, suggesting this is a promising model for translational placental toxicity testing.

Key words: placenta, pharmaceutical toxicology, pregnancy, alternatives to animal testing

Word count: 249, excluding title, authors, affiliations and keywords (max 250)