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Editorial

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Human Placentas and the Changing Face of Reproductive Toxicology Testing

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Pharmaceuticals are in use by 40-98% of pregnant mothers in the developed world, varying by country. There is a significant potential for obstetricians to further maintain medical prescriptions for chronic diseases during pregnancy, provided there is confidence within the pharmaceutical industry on the safety of their products. The safety of medicinal products incurs several socioeconomic challenges, and the protection of maternal and fetal health is a foremost and top priority. Current guidelines for reproductive toxicity testing in rats and rabbits provide the required data for international regulatory bodies, such as the Federal Drug Agency (FDA) and the European Medicines Agency (EMA) and are described by the Organization for Economic Cooperation and Development (OECD). These animal studies include fetal organ anthropometry, but are devoid of much fetal organ functional data, so there is a case for improving animal data quality during reproductive toxicity testing. Human placental models have a real potential to refine, or even replace some animal use in the pharmaceutical industry, by predicting the probability of unfavourable events for fetal growth and development and highlighting additional specific outcome measures to be used in rat and rabbit reproductive toxicology testing.

The pharma industry is engaging in a new drive for a revision of the regulations to include [new] "opportunities for modernising testing paradigms to enhance human risk assessment, while also potentially reducing animal use" (The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; ICH(S5) guidelines). In a recently published concept paper, the ICH consider the "development of basic principles for possible regulatory acceptance of *in vitro, ex vivo* and non-mammalian *in vivo* EFD assays". There has been a general recent discussion surrounding the values of alternatives to animal testing,[1,2] including a streamlined high-tech approach of developing an "organ on a chip".[3,4] These alternative methods would add an additional weight of evidence to pharma's *reproductive risk assessment protocols* prior to the inclusion studies of *Women of Child Bearing Potential* in clinical trials. In response to this call, the use of human placental models in safety evaluation may soon be on the horizon.

The placenta is orchestrated to respond to fetal needs during its growth and development. Whilst new emerging technology using zebra fish larvae is furnishing useful teratological assessments prior to the use of more complex *in vivo* mammalian models, this model lacks a placenta, therefore missing potential effects of pharmaceuticals on placental nutrient accretion, endocrinology, metabolism, xenobiotic transfer and haemodynamics; facets which have to be understood prior to the administration of a compound to a pregnant woman. A testing platform of theoretical (analytical and computational) and human placental experimental models could help bridge this information gap, ultimately helping obstetricians guide pregnant women who take medication for their chronic medical conditions.

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A momentum is building within Europe, developed by an association called *PlaNet* (placentology network), comprising of 25 EU centres from 15 countries with academic, clinical, industrial, standardisation and policy making backgrounds. Their academic expertise includes obstetrics, physiology, pharmacology, biophysics and mathematical modellers. *PlaNet's* objectives are to help provide better advice on the safety of medicinal products and environmental substances in pregnancy, create a pool of standards for human placenta toxicology test systems and explore the potential to deliver both cost savings and reductions in the number of animals used in reproductive toxicology safety testing. An evaluation of human placenta research systems is central to this initiative. Human placental tissue from a range of gestational ages is readily available to researchers with informed consent, where there is an established association with the Obstetric and Gynaecology Department. Proposed human placental test systems vary widely from the use of more simplistic placental barrier microvillous membrane vesicles, manufactured from the maternal blood-facing syncytiotrophoblast epithelium; to the most complex human *ex vivo* dual placental cotyledon perfusion model, most notably developed by Prof. Henning Schneider in the late 1960's/early 1970's and being continually enhanced today; most recently, to appropriate oxygenation to an unusually low normal soluble level found in this tissue *in utero*. A platform of human placental test systems has the potential to deliver meaningful data relating to xenobiotics transfer rates, uptake and pharmacokinetics; changes in nutrient and ion uptake; permeability dysregulation; alterations to endothelial and trophoblast signalling; fetoplacental vascular blood flow and resistance changes; disruption to placental angiogenesis and vasculogenesis; changes in paracrine signalling and placental barrier signal transduction; inflammation and immune modulation; trophoblast invasion and implantation; syncytiotrophoblast shedding commonly associated with the pathology of preeclampsia; DNA damage and repair; genotoxicity and carcinogenesis risk indicators. What is more, the human placenta is a unique organ, differing significantly from placentas of other species, both in structure and in function. Thus, the human placenta-based experimental and theoretical techniques have potential not only to refine and reduce the animal use in reproductive toxicological research, but also to strengthen the relevance of derived conclusions.

This moment of global rethinking on reproductive toxicity testing guidance appears to be a fitting juncture to consider standardising a human placental testing platform across research institutes internationally. It presents a real and exciting opportunity to develop mathematical modelling tools related to human placental function that will assist in our understanding of important factors such as xenobiotics transfer to the human fetus, their toxicological effects on nutrient and oxygen transfer and potential effects on placental haemodynamics, which could impinge on fetal growth and development. Most importantly, the time is ripe for academic researchers to engage with the pharma industry, which is currently challenged with slowing growth, but also outwardly looking for reinvention opportunities.

REFERENCES

1. Burden N, Sewell F, Chapman K. Testing chemical safety: what is needed to ensure the widespread application of non-animal approaches? *PLoSBiol*. 2015; 13: e1002156. doi: 10.1371/journal.pbio.1002156

2. Willyard C. The boom in mini stomachs, brains, breasts, kidneys and more. *Nature*. 2015; 523: 520. doi: 10.1038/523520a

3. Reardon S. 'Organs-on-chips' go mainstream. *Nature*. 2015; 523: 266. doi: 10.1038/523266a

4. Esch EW, BahinskiA, Huh D. Organs-on-chips at the frontiers of drug discovery. *Nat Rev Drug Discov*. 2015; 14: 248-260. doi: 10.1038/nrd4539