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Therapeutic interventions: The importance of including diseased and healthy samples in preclinical studies

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Preeclampsia is one of the most serious complications of pregnancy, diagnosed when a pregnant woman presents in the second half of pregnancy with hypertension, proteinuria and oedema. Sadly, it is responsible for significant maternal and perinatal morbidity and mortality, with the greatest burden experienced in the developing world. Preeclampsia causes widespread injury to many of the mother's organ systems including her blood vessels (hypertension), kidneys, liver, haematological system and brain. It can also cause fetal growth restriction [1].

Preeclampsia is believed to stem from poor placental invasion early in pregnancy [1]. The preeclamptic placenta releases elevated levels of injurious factors into the maternal circulation. These include anti-angiogenic factors and pro-inflammatory cytokines that cause maternal blood vessel injury [2]. The net result of this is systemic vascular dysfunction and end organ damage. A feature of endothelial dysfunction in preeclampsia is reduced bioavailability of nitric oxide (NO) activity. NO is a key factor contributing to vasorelaxation and lowering of blood pressure [3]. Thus, reduced vasorelaxation activity and enhanced vasoconstrictor influences impact upon the vascular smooth muscle and contribute to the hypertension that is characteristic of preeclampsia.

Given the only effective treatment for preeclampsia is delivery of the baby and placenta, there has been much interest in re-purposing therapies as a means to treat this disease. One such medication is sildenafil, a treatment widely used to treat erectile dysfunction. Sildenafil's main mechanism of action is as a phosphodiesterase-5 inhibitor that induces vasorelaxation. Indeed, in animal models, sildenafil has shown potential to improve both fetal and maternal pregnancy outcomes in preeclampsia models [4,5]. In humans, a randomised controlled trial suggested sildenafil reduces blood pressure, improves blood flow to the uterus and prolongs pregnancy in preeclamptic patients by 4 days, relative to placebo treated controls [6].

In an article in *EBioMedicine,* Hitzerd and others [7] have tested the effects of sildenafil in placentas and vessels obtained from human preeclamptic pregnancies. The team initially dissected the effects of sildenafil on vasorelaxation in arteries obtained from the fetal side of the placenta. The rationale for these studies was that if sildenafil was to be a beneficial treatment for preeclampsia, it should enhance vasorelaxation. In vessels obtained from healthy term pregnancies, Hitzerd and colleagues showed that sildenafil enhanced nitric oxide dependent vasorelaxation, whilst this effect was not observed in preterm preeclamptic vessels; suggesting differential effects of the drug on vasorelaxation in healthy versus diseased samples. The team also attempted to assess sildenafil transfer across the placenta in healthy and preeclamptic placentas using perfusion studies. They were limited in their study of preeclamptic placentas due to difficulties in perfusing preterm placentas, and thus did not attempt to perfuse gestation matched samples due to these same difficulties. In their small sample size of just two preterm preeclamptic placentas, they suggest that sildenafil transfer may be higher in preeclamptic placentas relative to term healthy controls.

Although interpretation of the placental transfer findings warrants caution due to very small sample numbers and varied gestation at placental collection, the findings from Hitzerd and colleagues raises important considerations for those working in the field of therapeutic discovery. In particular these findings highlight the need for testing therapeutics in both healthy and preeclamptic samples given the pathophysiology of the disease is likely to produce perturbations in signalling pathways important for therapeutic action. Moreover, consideration of placental transfer rates appears essential given the potential unknown effects of novel therapies on fetal wellbeing. Indeed, recently sildenafil was tested as a potential therapeutic for severe early onset fetal growth restriction in an international consortium of large multi-centre randomised controlled trials (the STRIDER study). The major reason for trialling sildenafil was its potential to enhance vasodilation and blood flow to the compromised feto-placental unit. Whilst no net-benefit of sildenafil was observed in the first two cohorts [8,9], the Dutch STRIDER trial was closed prematurely due to an increase in cases of pulmonary hypertension in the newborns [10].

Whilst the statistical analyses from the Dutch STRIDER trial following its cessation remain a work in progress, the effects of sildenafil on vascular reactivity and placental transfer rates in human fetal growth restriction have not been investigated. Thus, it appears essential that pre-clinical studies for novel therapies not currently used in pregnancy must carefully tease out the effects of drugs in both healthy and

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diseased samples, as well as considering placental transfer studies to determine the potential level of fetal exposure. Moreover, for those drug therapies that are known to be safe to administer during pregnancy, clarification of the amount of drug that reaches the placenta, and/or placental transfer that occurs, may be important considerations for future work and to inform dosage for clinical trials.

Declaration of Competing Interest

None.

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