**Evaluating Potential Treatments Targeting Angiogenesis in Preeclampsia**

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**Background and aims.** This study established a novel *in vivo* model of preeclampsia by inducing angiogenic imbalance (high sFlt-1/low FKBPL) (Figure 1) and evaluated the impact of potential treatments for preeclampsia in an *in vivo* model a.

**Methods.** Wild-type (WT) and *fkbpl+/-* C57BL/6N mice were administered sFlt-1 (5μg) using non-viral gene delivery system, RALA, as nanoparticles, intravenously on embryonic day (E)8 and 12 and randomly allocated to i) control(n=10), ii) exercise(n=5), iii) metformin(n=7) or iv) FKBPL-based peptide, AD-01(n=8) groups. Echocardiography and placenta/embryo weight were determined, and hearts/placentas/embryos were harvested on day E18.

**Results.** RALA-sFlt-1 (<100 nM, 40–60 mV) reduced embryo weight (*p*<0.0001) in WT (female/male: *p*<0.0001) and *fkbpl⁺/⁻* mice (female: *p*<0.05; male: *p*<0.01), compared to vehicle control. Exercise improved embryo weight only in sFlt-1 *fkbpl⁺/⁻*mice (female: *p*<0.001; male: *p*<0.0001). AD-01 improved embryo weight in sFlt-1 WT (female/male: *p*<0.05) but reduced it further in *fkbpl⁺/⁻*(female/male: *p*<0.01). Metformin had no effect. Placental efficiency was reduced in WT with RALA-sFlt-1 (female: *p*<0.01; male: *p*<0.001) but not in *fkbpl+/-* mice. Nevertheless, in sFlt-1 *fkbpl⁺/⁻* mice, exercise increased placental efficiency (female: *p*<0.001; male: *p*<0.05), while AD-01 decreased it (female: *p*<0.05; male: *p*<0.01). Placental sFlt-1 levels were reduced in sFlt-1 *fkbpl⁺/⁻*females (*p*<0.01), trended higher in sFlt-1 WT (*p*=0.07), compared to vehicle controls; exercise further decreased placental sFlt-1 concentration in *fkbpl⁺/⁻*(female: *p*<0.05; male: *p*<0.01). Metformin had no effect. Pregnancy increased cardiac output in WT vs. non-pregnant controls (*p*<0.0081), but sFlt-1 reduced it (*p*<0.044). In WT mice, exercise restored cardiac output (*p*<0.0015); metformin showed a trend (*p*<0.054). Metformin reduced cardiac sFlt-1 levels in *fkbpl⁺/⁻* mice compared to the sFlt-1 *fkbpl+/-*control mice (*p*<0.035).

**Conclusion/Discussion.** Our nanoparticle-induced preeclampsia model of angiogenic imbalance impairs maternal cardiovascular and fetal outcomes; exercise, metformin, and AD-01 show variable and *fkbpl*-dependent therapeutic effects.

**References:**

 a McNally R, Alqudah A, McErlean EM, Rennie C, Morshed N, Short A, McGrath K, Shimoni O, Robson T, McCarthy HO, McClements L. Non-viral gene delivery utilizing RALA modulates sFlt-1 secretion, important for preeclampsia. Nanomedicine. 2021 Sep 1;16(22):1999-2012.



**Figure 1**.**Schematic illustration of the animal work (ETH 22-7673).** Female FKBPL knocked down mice (one copy of FKBPL knocked down, (fkbpl+/-) and wild-type control (fkbpl+/+) female mice with fkbpl+/+ male mice mating. Female mice will then receive sFlt-1 containing nanoparticles on day 8 and day 12 of gestation to induce preeclampsia phenotype and blood pressure will be measured on gestational days 8, 12, 14, 16, and 18 (before sacrifice). Simultaneously at day 8 of gestation, the mice will be administered potential treatments before collection of blood and tissue samples at the endpoint at day 18 of gestation. Figure produced in Biorender.