ABSTRACT

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Depression is a serious mental disorder affecting 10-20% of women during pregnancy. Up to 10% of these pregnant women are prescribed antidepressants (ADs), most frequently from the class of selective serotonin (5-HT) reuptake inhibitors (SSRIs). While the safety of this treatment is questionable due to reported impaired pregnancy/fetal outcomes, understanding of potential mechanistic causes is still lacking. During pregnancy, 5-HT is important for normal placental function and proper fetal development and programming. 5-HT homeostasis in the placenta is maintained via the 5-HT transporter (SERT/*SLC6A4*) on the apical side and the recently characterized organic cation transporter 3 (OCT3/*SLC22A3*) on the basal side of trophoblast. These transporters take up 5-HT from the maternal and fetal circulations, respectively into the syncytiotrophoblast (STB) where it is degraded by monoamine oxidase-A (MAO-A). As all ADs interfere with the 5-HT system it is important to study their potential interactions in the feto-placental unit.

Experiments were carried out *in situ* (dually perfused rat term placenta) and *ex vivo* (membrane vesicles isolated from human term placenta). The inhibitory potential of paroxetine, citalopram, fluoxetine, fluvoxamine, sertraline and venlafaxine on 5-HT uptake by placenta was tested. In both models, we observed significant inhibitory potential of selected ADs on SERT and OCT3 mediated transport of 5-HT. In addition, in the rat placenta we observed a pronounced effect of fetal gender on AD-mediated inhibition of OCT3.

Our study suggests that use of ADs in pregnancy may affect both SERT and OCT3 responsible for 5-HT uptake from maternal and fetal circulations, respectively. This could result in disrupted 5-HT homeostasis in the feto-placental unit and thus local toxicity due to the vasoconstrictive properties of 5-HT.