The use of GLP-1 agonists and SGLT2 inhibitors during pregnancy and lactation: a systematic review of the evidence

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Background
Glucagon-like peptide 1 receptor agonists (GLP-1RA) and sodium-glucose co-transporter-2 inhibitors (SGLT2i) are novel drugs for the treatment of type 2 diabetes mellitus. Their use during pregnancy and lactation is discouraged, however few data are available. The aim of the present study is to systematically review all available data on the safety of GLP-1RA and SGLT2i during this period.
Methods
PubMed, clinicaltrials.gov and FDA as well as EMA product information were searched up to June 2020 using terms for current GLP-1RA and SGLT2i combined with terms for pregnancy, lactation and diabetes. 14 animal and 8 human studies on GLP1-RA and 9 animal and 5 human studies on SGLT2i were included.
Results
In animal studies, use of all GLP-1RA caused reduced fetal weight and/or growth, delayed ossification and skeletal variants usually accompanied by a reduction in maternal weight. Visceral abnormalities and skeletal malformations were seen with liraglutide as well as semaglutide. In animal studies exendin-4 was shown to not diffuse through the maternal-fetal interface in the absence of systemic inflammation. Exenatide showed a fetal-to-maternal peptide concentration ratio of ≤ 0.017 in ex vivo placental perfusion. In animal studies SGLT2i were generally safe during the first trimester but exposure during the period coinciding with the late second and third trimester of human renal development, caused dilatation of the renal pelvis and tubules. In animal studies GLP-1RA and SGLT2i are excreted in breast milk, human data are not available.
Discussion/Conclusion
Exendin-based GLP-1RA and albiglutide do not cross the placenta. Harmful fetal effects seen while using these drugs are therefore likely caused by caloric restriction induced in the mother. SGLT2i show adverse effects on the developing kidney in animal studies, confirming the advice to discontinue these during pregnancy and lactation since human kidney maturation continues during the first 2 years of life.