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Safety of medicines and case reports

Pregnancy outcomes after GLP-1 agonist exposure in early pregnancy

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Introduction

Glucagon-like peptide 1 (GLP-1) agonists, including dulaglutide, exenatide, semaglutide, liraglutide, albiglutide and beinaglutide, are extensively used for the management of type 2 diabetes mellitus. Beyond their use in improving blood glycaemic control, some GLP-1 agonists are also used for facilitating weight reduction among individuals with excess weight.

These medications are also commonly prescribed for women of reproductive age. In a Swiss administrative claim database study, GLP-1 receptor agonists accounted for approximately 20% of the prescribed blood glucose-lowering medications in pregnancies where antidiabetic medications were dispensed for pregestational diabetes mellitus (1). Given that many pregnancies are unplanned, there has been an increasing number of unexpected exposures to these drugs during the early stages of pregnancy. Consequently, the Swiss Teratogen Information Service (STIS) and other Teratology Information Services (TISes) worldwide, are observing an increasing number of requests concerning the potential risks associated with these drugs in early pregnancy. At present, providing guidance to these patients and their healthcare providers is challenged by the limited availability of data. Regarding liraglutide, a single case of exposure during the first trimester of pregnancy has been documented, with a favourable outcome observed for the newborn (2). Furthermore, an exenatide pregnancy registry recorded seven cases of exposure during pregnancy, although comprehensive follow-up information remains unavailable (3).

GLP-1 agonists are characterised by a large molecular size, ranging from 3,700 Da (liraglutide) up to 63,000 Da (dulaglutide): placental transfer is not expected a priori, unless specific mechanisms exist. However, findings from animal studies indicate the potential for reproductive toxicity at doses causing polymorphic maternal toxicity for semaglutide, dulaglutide, exenatide and liraglutide. For liraglutide and semaglutide, an increased risk of birth defects (fetal vessel, kidney, liver and skeletal abnormalities) was observed at doses equivalent to those administered in humans (4–6).

Given the limited availability of data, we intended to investigate whether GLP-1 agonists were associated with adverse pregnancy outcomes. This led us to initiate a multicentre, prospective, observational cohort study involving members of the European Network of Teratology Information Services (ENTIS). ENTIS, a non-profit organisation that coordinates TIS activities, is dedicated to providing evidence-based information to patients and their caregivers concerning medication safety and risks during pregnancy and breastfeeding. TISes collect patient data, including information on pregnancy outcomes. This promotes collaborative research that contributes significantly to our understanding of risks associated with drugs during pregnancy.

Methods

This prospective, observational cohort study was conducted involving seven participating centres in six countries: Australia, Germany, Israel, Italy, Switzerland and the United Kingdom. We studied pregnant women exposed to GLP-1 agonists during the first trimester. We compared their pregnancy outcomes to two reference groups: one with diabetes exposed to non-GLP-1 agonist antidiabetic drugs, and another of overweight or obese patients

exposed to non-teratogenic drugs. Data collection involved two phases: initial contact with the TIS and post-expected delivery date. We used standardised questionnaires given to patients or their healthcare providers to gather information. This included maternal characteristics, medical history, drug exposure details and concurrent medications during the first TIS contact. After the expected delivery date, follow-up was carried out through structured questionnaires and telephone interviews to obtain data on pregnancy outcomes, gestational age, birth weight, birth defects and neonatal complications. Birth defects were classified using the European Network of Population-based Registries for the Epidemiological Surveillance of Congenital Anomalies (EUROCAT) ICD10-BPA system (7).

Preliminary results

Whilst the analysis is ongoing, preliminary results based on data from 173 pregnant women exposed to a GLP-1 agonist during the first trimester of pregnancy, along with two reference groups (comprising pregnant women with diabetes and overweight or obese pregnant women), suggest that there is neither a significant increase in the rate of major birth defects nor in the risk of pregnancy loss for women exposed to GLP1 agonists.

Discussion

To the best of our knowledge, this observational prospective multicentre study represents the first evaluation of the reproductive safety of early pregnancy exposure to GLP-1 agonists. ENTIS is in a unique position to conduct independent post-marketing surveillance of drugs during pregnancy. Given the scarcity of data on drug exposure in pregnancy, which often takes considerable time to emerge in the literature, studies like this prospective multicentre cohort investigation are essential for enhancing our understanding of the potential risks. We would like to highlight that the detailed analysis of our findings is currently underway, and we anticipate publishing the full results in the near future.

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