The need for appropriate registration of pregnancy outcomes under newer oral glucose-lowering therapies

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Abstract

Due to the increase of type 2 diabetes (T2DM) in young adults, women of childbearing age are frequently treated with newer glucose-lowering therapies and an increase of unintentional exposure to therapies unapproved for use during pregnancy is expected. The clinician is left with the dilemma whether stopping novel agents giving excellent glycemic control is the best thing to do as switching to other agents may cause deterioration of glycemia, while continued use of novel agents may have uncertain effects on the unborn child. For T2DM, pregnancy data are only collected via spontaneous reporting systems. We evaluated therefore the available data on pregnancy outcomes under newer glucose-lowering agents in pharmaceutical safety databases. We show that data on pregnancy outcomes with new glucose-lowering agents in T2DM are scarce, with a high risk for bias towards negative outcomes, limiting their usefulness to robustly assess safety. Due to lack of information, at present, these agents are not recommended for use during pregnancy or when planning pregnancy.' To better guide clinical practice, structured systems of assessing pregnancy outcomes in women receiving these novel agents are urgently needed.

Background

Since type 2 diabetes (T2DM) becomes more prevalent and affects people at a younger age, the number of women with T2DM of childbearing age will increase. In many countries, the proportion of pregnant women with T2DM has risen to nearly half of all cases of pregnancies with diabetes, with T2DM outnumbering type 1 diabetes (T1DM) pregnancies in some metropolitan areas (1). Women with T2DM are at equally high risk for adverse pregnancy outcomes, such as congenital anomalies and stillbirths as those with T1DM (1). Preconception care with the aim of optimizing glycemic control, can reduce adverse pregnancy outcomes (1). While for women with T1DM preconception care is facilitated through the follow-up at diabetes services, the uptake of preconception care is often poor in women with T2DM. In addition, many pregnancies in women with T2DM are unplanned (2,3).

Due to potential implications of transplacental passage of oral glucose-lowering agents on the developing fetus and due to the long-standing experience and efficacy of insulin in pregnancy, insulin is generally recommended as the first choice treatment in pregnancy to achieve good glycemic control (4). Experience with oral hypoglycemic agents in pregnancy, such as metformin and glibenclamide, is mostly retrieved from women with gestational diabetes (5,6). In addition, there is a paucity of long-term follow-up data on children exposed to these agents in utero (7). Recent data suggest significantly increased rates of overweight and obesity in a 4-year offspring cohort to mothers with polycystic ovarian syndrome exposed to metformin in pregnancy compared to non-exposed women (8).

Women with T2DM of childbearing age are now frequently treated with newer oral diabetes therapies such as dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium glucose co-transporter 2 (SGLT-2) inhibitors. In general, preclinical reproduction studies in rats with

79 DPP-4 inhibitors, have indicated no evidence of impaired fertility or teratogenicity.
80 However, there have been reports of growth retardation, delayed ossification and
81 miscarriage in pregnant rats and rabbits treated with DPP-4 inhibitors (9). Studies in rats
82 treated with SGLT-2 inhibitors have shown toxicity in developing kidneys with an increased
83 incidence and/or severity of renal pelvic and tubular dilatations in the time- period
84 corresponding to the second and third trimesters of human pregnancy (9). In addition, in
85 animal studies, as mentioned in the labels for DPP-4 inhibitors and SGLT2-inhibitors, these
86 agents have shown to cross the placenta and to be excreted into breast milk. However,
87 reports on safety and outcomes in pregnant women exposed to these newer glucose-
88 lowering agents are very scarce or non-existing. A recent cohort study in women with
89 pregestational diabetes (40% with T2DM) based on a primary care medical history database
90 from 1995 to 2012, evaluated the adverse fetal outcomes in 311 pregnant women on non-
91 insulin glucose-lowering agents during the first trimester compared to 833 women on
92 insulin. The study showed that the use of non-insulin agents early in pregnancy was not
93 associated with greater risks of fetal losses or major malformations than insulin (10).
94 Although the evaluated non-insulin glucose-lowering agents included sulfonylureas (SU),
95 glitazones, DPP-4 inhibitors and glucagon like-peptide-1 (GLP-1) agonists, metformin
96 represented most of the oral medication use and no women received treatment with SGLT2-
97 inhibitors (10).
98 Due to the lack of prospective studies in pregnancy, newer oral glucose-lowering agents are
99 not indicated for use in pregnancy. For T2DM, data for unintentional use during pregnancy
100 are only collected beyond clinical studies via spontaneous reporting systems since health
101 authorities do not request reporting through mandatory registries. Any individual, health
102 care professional, patient or an employee of a pharmaceutical company when learning

about an adverse event, must report this event as off-label use and/or a pregnancy in a women taking medication, which is not approved for use during pregnancy, to the manufacturer of the drug or health authorities within 24 hours. For pregnancies and T2DM, the reported cases and outcomes are, as for any adverse events, summarised parts of periodic safety update reports and other regular pharmacovigilance activities. We evaluated therefore the available data on pregnancy outcomes under new oral glucose-lowering agents not indicated for use during pregnancy in pharmaceutical company safety databases.

Methods

We chose to evaluate the most recent SU, gliclazide and the most commonly used glitazone, pioglitazone, in addition to all available data for DPP-4 inhibitors and SGLT2-inhibitors. In October 2017, we contacted therefore the following pharmaceutical companies: Servier, Takeda, Novartis, Boehringer-Ingelheim, Janssen, MSD and AstraZeneca, with the request to provide us with data on the number of reported pregnancies and their outcomes under the following agents: Gliclazide, pioglitazone, the DPP-4 inhibitors alogliptin, vildagliptin, saxagliptin, linagliptin, sitagliptin and the SGLT2-inhibitors canagliflozin, empagliflozin and dapagliflozin. The search of reported pregnancies under these glucose-lowering agents in the safety databases was performed by the pharmaceutical companies using MedRA version 19.1 and included data from controlled clinical trials, post-marketing surveillance studies and spontaneous reports. The number of pregnancies reported, the maternal outcomes (including number of live births), preterm deliveries (premature delivery, premature labor, premature newborn, emergency cesarean sections), abortions and neonatal outcomes (including the number of congenital anomalies, other complications or deaths), were analyzed and presented as descriptive data.

Results

Table 1 gives an overview of the number of reported pregnancies and number of reported pregnancy outcomes under new oral glucose-lowering agents, which are not indicated for use in pregnancy, available in the pharmaceutical company safety databases. The following pharmaceutical companies: Servier, Takeda, Novartis, Boehringer-Ingelheim, Janssen, MSD and AstraZeneca contributed with data, while the pharmaceutical company Servier was only willing to report the number of reported pregnancies under the SU gliclazide but not the pregnancy outcomes. A total of 479 pregnancies in women with T2DM were reported with a variation of the reported pregnancies between 25 and 130 cases per agent. The number of reported pregnancies with outcomes varied from 2 to 69 per agent. Many reported pregnancies lacked data on the outcomes since only 50.6% (n=224) of all reported pregnancies had reported pregnancy outcomes. Of all reported pregnancy outcomes, 54.0% (n=121) reported uncomplicated, healthy live births.

Conclusions

We show now that data on pregnancy outcomes in women with T2DM and treated with newer oral glucose-lowering agents, which are not indicated for use in pregnancy, are scarce and incomplete due to underreporting. In addition, due to often retrospective nature of reporting and the fact that uncomplicated pregnancies are less often reported, there is a high risk for bias towards negative outcomes. An important reason for the limited available information is that data on pregnancies in T2DM are currently only based on spontaneous reporting systems. Uneventful pregnancy outcomes under new agents are therefore only rarely reported. For instance, the number of congenital malformations and abortions for pioglitazone were very high. Caution is therefore warranted for misinterpretation as these data, although useful, have limited use to robustly assess the safety of these agents, which

151 are not indicated or properly studied for use during pregnancy. However, due to the
152 increased prevalence of T2DM in women of childbearing age, the low uptake of
153 preconception planning in women with T2DM and the increased use of new glucose-
154 lowering agents in women of childbearing age, unintentional first-trimester exposure to
155 these new agents will further increase. In addition, long-term follow-up data on children
156 exposed to these agents in utero are needed. Due to lack of adequate evidence to guide
157 clinical practice, the clinician is currently left with the dilemma- whether stopping novel
158 agents that give excellent glycemic control in a woman with T2DM is the best thing to do as
159 switching to other agents may cause deterioration of glycemia and all undesirable effects for
160 pregnancy while continued use of the novel agents may have uncertain effects on the
161 unborn child (acute and in later life). Until more evidence becomes available on the safety of
162 unapproved diabetes agents in pregnancy, these agents are not recommended for use
163 during pregnancy or when planning pregnancy. Preconception counselling in women with
164 T2DM is mandatory but challenging as many T2DM pregnancies are unplanned. When
165 women become pregnant under unapproved diabetes agents, a shift to insulin treatment
166 and more frequent ultrasounds to assess congenital malformations can be recommended.
167 Currently, no strict rules for follow-up exist and clinicians are less good at reporting any
168 outcomes of pregnancy after unintentional exposure to new glucose-lowering therapies. We
169 are therefore confronted with the absence of essential data and failure of present systems
170 to adequately gather information on safety in pregnancy of these new glucose-lowering
171 agents. Moreover, solid data based on prospective observational cohort studies with
172 appropriate controls in the first trimester of pregnancy may also be needed for older
173 diabetes agents such as metformin. In addition, prospective studies such as randomized
174 clinical trials (RCT) are not the best method or ethically justifiable for evaluating rare events

such as congenital malformations and perinatal/neonatal mortality. Such RCTs are, however, not feasible, as they would necessitate very large sample sizes for sufficient power to evaluate the impact of new diabetes therapies on pregnancy outcomes. Population reports have reported outcome incidences but not in relation to specific treatments (11). Recently, the European Medicines Agency (EMA) has requested a post-authorization safety study be performed to monitor the long-term safety of insulin detemir in pregnant women (12). A large international prospective observational cohort study was therefore initiated to assess the safety of insulin detemir compared with other types of insulin during pregnancy (12). In the past, pregnancies in women with T2DM were considered not frequent and health authorities recommended therefore that pregnancy data in T2DM should only be collected via spontaneous reporting systems. These recommendations should be revised as T2DM in pregnancy is increasing rapidly worldwide. Therefore, there is a need to explore structured systems of assessing pregnancy outcomes in women receiving novel agents for diseases as this can provide information to guide clinical practice. Well-designed registries might be useful for prospective registration of pregnancy outcomes for assessment of safety and an attempt to detect rare events under unintentional first trimester exposure with new glucose-lowering agents, including oral hypoglycemic agents and injectables, which are not indicated for use in pregnancy. These registries could also collect long-term follow-up data on children exposed to these agents in utero. Teratology information services might help as cooperating experts for the evaluation of adverse drug reactions of antidiabetics during pregnancy.

In addition, increased awareness is required among health care professionals and pharmaceutical companies for the need of adequate reporting of pregnancies after unintentional exposure to newer glucose-lowering agents. The availability of easy- to- use

199 registries might facilitate reporting of pregnancy outcomes for new agents and would
200 provide much needed information to guide clinical practice. An interdisciplinary
201 collaboration between diabetologists and experts in the design and analysis of prospective
202 observational studies of unlicensed drugs for pregnant women could significantly improve
203 the power of such registries. We feel that such registries might best be developed and
204 centralized by authorities such as by EMA and the US Federal Drug Administration (FDA).

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218 **Table 1. The number of pregnancies and pregnancy outcomes following unintentional**
219 **exposure to oral glucose-lowering agents reported in pharmaceutical safety databases**

	Data cut-off	Number of pregnancies reported	Number of Pregnancies with outcomes reported	Reported Pregnancy outcomes
Gliclizide	26-2-2016	36	NA	NA
Pioglitazone	9-11-2017	131	61	18 spontaneous abortions, 8 congenital anomalies, 3 induced abortions, 1 growth retardation, 31 healthy infants
Alogliptin	9-11-2017	25	18	4 spontaneous abortions, 3 induced abortions, 2 foetal deaths, 1 ectopic pregnancy, 1 fetal chromosomal abnormality, 1 foetal enlarged kidney, 6 healthy infants
Vildagliptin	30-11-2016	130	69	2 congenital anomalies (renal and anal aplasia with single umbilical artery and a patent ductus arteriosus), 15 abortions, 54 live births
Linagliptin	2-5-2017	33	14	2 congenital anomalies (patent ductus arteriosus and holoprosencephaly with induced abortion), 1 sponaneous abortion, 4 induced abortions, 1 miscarriage, 1 stillbirth, 1 large for date baby
Sitagliptin	3-8-2016	74	30	10 spontaneous abortions, 1 elective abortion, 2 live births with birth defects (1 cleft lip and palate, 1 multicystic dysplastic kidney and hypoplastic adenohypophysis and ectopic neurohypophysis), 18 healtly live births
Saxagliptin	31-1-2018	15	2	1 elective abortion, 1 premature baby (healthy)
Canagliflozin	28-3-2017	29	13	1 congenital anomaly, 2 abortions, 1 fetal demise, 8 normal live births and 2 ongoing pregnancies
Empagliflozin	17-4-2017	21	9	2 sponaneous abortions, 1 elective termination, 1 ectopic pregnancy, 3 live births without congenital anomaly, 1 premature baby
Dapagliflozin	31-8-2018	21	8	1 congenital hydrocephalus, 1 encephalocoele, 1 fetal encephalocoele, 1 non-healthy baby with talipes, renal aplasia and oesophageal atresia, 2 elective abortions, 1 premature baby (healthy), 1 healthy baby

220 NA: not available

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Conflict of Interest Statement

PP is an employee and shareholder of a pharmaceutical company, Novartis Pharma AG, but no potential conflicts of interest relevant to the article are present. KB, EM and CM have no competing interests concerning the article.

Author contributions

All authors contributed to the design of the study, KB, PP and CM collected the data, KB did the analysis of the data and all authors contributed to writing of the paper.