ABSTRACT

Introduction We previously reported an increased risk of being small for gestational age (SGA) and a decreased risk of being large for gestational age (LGA) after in utero exposure to metformin compared with insulin exposure. This follow-up study investigated if these observations remain when metformin exposure (henceforth, metformin cohort) is compared with non-pharmacological antidiabetic treatment of gestational diabetes mellitus (GDM; naïve cohort), instead of insulin.

Research design and methods This was a Finnish population register-based cohort study from singleton children born during 2004–2016. Birth outcomes from metformin cohort (n=3964) and the naïve cohort (n=82675) were used in the main analyses. Additional analyses were conducted in a subcohort, restricting the metformin cohort to children of mothers with GDM only (n=2361). Results were reported as inverse probability of treatment weighted OR (wOR), with the naïve cohort as reference.

Results No difference was found for the outcome of SGA between the cohorts in the main analyses (wOR 0.97, 95% CI 0.73 to 1.27) or in the additional analyses (wOR 0.97, 95% CI 0.75 to 1.37). No difference between the cohorts was found for the risk of LGA (wOR 0.91, 95% CI 0.75 to 1.11) in the main analyses but a decreased risk was observed in the additional analyses (wOR 0.72, 95% CI 0.56 to 0.92).

Conclusions This follow-up study found no increase in the risk of SGA or LGA after in utero exposure to metformin, compared with drug-naïve GDM. The decreased risk of LGA in mothers with GDM may suggest residual confounding. The lack of increased SGA risk aligns with findings from studies using metformin in non-diabetic pregnancies. In contrast, lower birth weight and increased SGA birth risk were observed in GDM pregnancies for metformin versus insulin. Metformin should be avoided with emerging growth restriction in utero. The interplay of intrauterine hyperglycemia and pharmacological treatments needs further assessment.

INTRODUCTION

Metformin use in pregnancy is increasing worldwide, both for continued use in pregnant women with underlying type 2 diabetes mellitus (T2DM) and for gestational diabetes mellitus (GDM). Metformin is also commonly prescribed off-label in women with polycystic ovary syndrome (PCOS) to induce ovulation and to improve pregnancy outcomes. Metformin crosses the placenta, exposing the fetus to plasma concentrations comparable to maternal circulations. However, several studies reported the effectiveness of metformin for glycemia control without short-term adverse effects and with additional potential benefits in the neonatal period. In early 2022, European Health...
authorities approved the use of metformin during pregnancy and in the periconceptional period for the originator metformin product (Glucophage, Merck KGaA, Darmstadt, Germany). This change was, at least in part, based on the large register-based cohort (main CLUE study), in which maternal pregnancy exposure to metformin was studied and both short-term and long-term adverse outcomes in children (up to 11 years after birth) were assessed. The study found no increased long-term risk associated with pregnancy exposure to metformin. However, an increased risk of being small for gestational age (SGA) and a decreased risk of children being large for gestational age (LGA) after in utero exposure to metformin in comparison to in utero exposure to insulin was found. Similar results were observed in children born to mothers with GDM and naïve to in utero exposure to non-pharmacological antidiabetic treatment compared with in utero exposure to insulin.

We hypothesized from our previous study results that the observed increased risk of SGA and decreased risk of LGA may be related to the choice of insulin as the reference for comparison, given the known association between insulin and weight increase. Based on these findings and to further strengthen the evidence, this follow-up study was performed to investigate if metformin is associated with increased risk of SGA and decreased risk of LGA when compared with non-pharmacological antidiabetic treatment exposure.

METHODS
This was a follow-up study performed on our previously published population-based register data cohort study. The study population included singleton children born to women, 18–45 years of age at the time of delivery, in Finland during 2004–2016. The children were identified using the Finnish Medical Birth Register, which holds information on all births in Finland, including date of birth, gestational age and birth weight. The start date of pregnancy was calculated by subtracting gestational age (recorded in weeks and days) from the date of delivery to obtain the date of the last menstrual period (LMP). The main analyses included two cohorts: children with in utero exposure to metformin (metformin cohort) regardless of the indication (ie, GDM, pregestational T2DM or PCOS) and children of mothers with GDM with non-pharmacological antidiabetic treatment (naïve cohort) (described in online supplemental item 1).

Exclusion criteria were maternal diagnosis of type 1 diabetes mellitus, maternal dispensation of systemic glucocorticoids during pregnancy (agents in this drug class are known to interfere with metformin) and maternal dispensation of antidiabetic medications other than metformin (anatomical therapeutic code (ATC) A10BA02) and insulin (ATC A10A) during pregnancy. To ensure adequate capture of information on exposure and baseline characteristics, children born to women not registered in Finland throughout the entire duration of pregnancy were excluded. Information on the selection of the study population and definitions of exclusion criteria are provided in online supplemental item 2 and 3.

Furthermore, a metformin-GDM subcohort was created for additional analyses. This subcohort was identified by excluding women who were assumed to use metformin in the treatment of T2DM or PCOS (details provided in online supplemental item 1).

Maternal exposure to metformin and to other pharmacological antidiabetic treatment was defined as having any dispensed prescription between the LMP and the date of delivery obtained from the Finnish Prescription Register. Information to identify children with LGA (birth weight 2 SD above the gestational age-specific and sex-specific reference mean in Finland) and SGA (birth weight 2 SD below the gestational age-specific and sex-specific reference mean) was ascertained from the Medical Birth Register.

The data sources used to identify covariates were the Medical Birth Register, the Prescription Register, the Care Register for Healthcare (HILMO), the Register of Primary Healthcare Visits (AvoHILMO), regional laboratory databases and Statistics Finland. A detailed description of the methods and covariate definitions is available in our previous publication.

The analyses of SGA and LGA were conducted using logistic regression to estimate ORs with 95% CIs, with naïve cohort as the reference. Inverse probability of treatment weighting (IPTW) with stabilized weights based on propensity scores (PS) was used to control for confounding. Separate PS models were estimated for the main analyses with metformin cohort and naïve cohort; and for the additional analyses with metformin-GDM subcohort and naïve cohort. Analyses were conducted after trimming of children outside the overlapping range of the PS. The predictors of the PS models were a broad range of covariates describing the mothers and pregnancies, including demographic factors, comorbidities before and during pregnancy, lifestyle factors, gestational week of GDM diagnosis, region of residence for the child and calendar year of delivery. The standardized mean difference was used to assess covariate balance between cohorts after weighting. Covariates that were not balanced after weighting (standardized mean difference ≥0.1) were included as independent variables in the outcome models.

RESULTS
A total of 3964 children in the metformin cohort and 82675 children in the naïve cohort fulfilled the criteria for inclusion in the main analyses (table 1 and online supplemental item 4). The metformin-GDM subcohort consisted of 2361 children. In the main analyses, 1070 (27.0%) children in metformin cohort and 233 (0.3%) in naïve cohort were excluded due to non-overlapping PS. The corresponding numbers for the metformin-GDM...
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Metformin cohort (n=3964)†‡</th>
<th>Naïve cohort (n=82675)‡</th>
<th>Standardized difference* Before IPTW</th>
<th>After IPTW§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age at birth (weeks), median (IQR)</td>
<td>39.4 (38.6–40.3)</td>
<td>39.9 (39.0–40.7)</td>
<td>Not included in propensity score</td>
<td></td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>1883 (47.5%)</td>
<td>39,624 (47.9%)</td>
<td>Not included in propensity score</td>
<td></td>
</tr>
<tr>
<td>Year of birth, n (%)</td>
<td>2081 (52.5%)</td>
<td>43,051 (52.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age at delivery, median (IQR)</td>
<td>32.0 (28.0–35.0)</td>
<td>31.0 (27.0–35.0)</td>
<td>0.223</td>
<td>–0.016</td>
</tr>
<tr>
<td>Maternal smoking during pregnancy, n (%)</td>
<td>29.7 (25.0–34.7)</td>
<td>26.9 (23.6–31.2)</td>
<td>0.697</td>
<td>0.056</td>
</tr>
<tr>
<td>Maternal comorbidities before pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregestational T2DM, n (%)</td>
<td>154 (3.9%)</td>
<td>N/A††</td>
<td>Not included in propensity score</td>
<td></td>
</tr>
<tr>
<td>PCOS, n (%)</td>
<td>463 (11.7%)</td>
<td>1164 (1.4%)</td>
<td>0.014</td>
<td>0.030</td>
</tr>
<tr>
<td>Obesity at the beginning of pregnancy, n (%)</td>
<td>486 (12.7%)</td>
<td>1164 (1.4%)</td>
<td>0.012</td>
<td>0.038</td>
</tr>
<tr>
<td>Pre-eclampsia in pregnancy, n (%)</td>
<td>1915 (2.3%)</td>
<td>0.076</td>
<td>0.024</td>
<td></td>
</tr>
<tr>
<td>Gestational week of maternal gestational diabetes diagnosis, median (IQR)‡‡§§</td>
<td>24.4 (15.0–27.7)</td>
<td>28.3 (25.1–34.4)</td>
<td>0.726</td>
<td>0.107</td>
</tr>
<tr>
<td>Essential hypertension in pregnancy, n (%)</td>
<td>58 (1.5%)</td>
<td>415 (0.5%)</td>
<td>0.096</td>
<td>0.009</td>
</tr>
<tr>
<td>Any toxemia in pregnancy, n (%)¶¶</td>
<td>557 (14.1%)</td>
<td>9842 (11.9%)</td>
<td>0.071</td>
<td>0.005</td>
</tr>
<tr>
<td>Pre-eclampsia in pregnancy, n (%)</td>
<td>2917 (3.5%)</td>
<td>0.035</td>
<td>0.034</td>
<td></td>
</tr>
<tr>
<td>Other characteristics</td>
<td>Persistence of diabetes in the mother after birth</td>
<td>60 (1.5%)</td>
<td>64 (0.1%)</td>
<td>Not included in propensity score</td>
</tr>
</tbody>
</table>

*The distributions of the variables used in propensity score weighting were compared between exposure groups (metformin-only exposure: yes/no), by means of standardized difference of prevalence (binary variable), standardized difference of mean (continuous variable) or Mahalanobis distance (categorical variables with more than two levels).
†3967 children in metformin cohort were included in the original CLUE manuscript but in this follow-up study three children were excluded because of unknown information on the outcomes (SGA/LGA). See online supplemental item 2 for specific details.
‡Before IPTW being applied.
§Numbers ≥0.1 are in bold, meaning the variable was not balanced after IPTW.
¶Information missing for 49 (1.2%) children in the metformin cohort and 1952 (2.4%) in the naïve cohort.
**BMI was categorized as ≤18.5, 18.6–25.0, 25.1–30.0 and >30.0.
††Previously diagnosed T2DM variable is by definition ‘no’ for all patients in the naïve cohort.
‡‡Gestational week of maternal gestational diabetes diagnosis was categorized as: <12; 12–19; 20–23; 24–26; 27–30; >30; GDM detected, time unknown and no diagnosis of gestational diabetes.
§§Information missing for 1132 (28.6%) children in the metformin cohort and 9515 (11.5%) in the naïve cohort.
¶¶Named after and including primary care ICPC-2 Code W81 (toxemia in pregnancy) in addition to secondary care ICD-10 code O10-16 (all edema, proteinuria and hypertensive disorders in pregnancy).
BMI, body mass index; GDM, gestational diabetes mellitus; ICD-10, International Classification of Diseases, Tenth Revision; ICPC, International Classification of Primary Care; IPTW, inverse probability of treatment weighting; LGA, large for gestational age; N/A, not available; PCOS, polycystic ovary syndrome; SGA, small for gestational age; T2DM, type 2 diabetes mellitus.
subcohort and naïve cohort in the additional analyses were 11 (0.5%) and 5808 (6.1%), respectively.

The median for gestational age at birth was 39.4 weeks in the metformin cohort and 39.9 weeks in the naïve cohort (table 1). In the metformin cohort, 43.6% of children were born during the latest time period (2014–2016) and 15.3% during the earliest time period (2004–2008), whereas in the naïve cohort 30.1% of births were born in 2014–2016 and 28.7% in 2004–2008. Maternal median age at delivery was 32 years in the metformin cohort and 31 years in the naïve cohort, while maternal prepregnancy body mass index (BMI) median was 29.7 kg/m² in the metformin cohort vs 26.9 kg/m² in the naïve cohort.

Most covariates included in the PS models were balanced after applying IPTW (standardized mean difference <0.1), however gestational week of maternal GDM diagnosis and PCOS remained unbalanced (table 1). GDM was diagnosed earlier in the metformin cohort and later in the naïve cohort (median of 24.4 gestational weeks and 28.3 gestational weeks, respectively) and PCOS frequency was higher in the metformin cohort (11.7%) than in the naïve cohort (1.4%). Both variables were, accordingly, included as adjusting variables in subsequent outcome models.

SGA was found in 2.3% of the children in the metformin cohort and 2.2% in the metformin-GDM subcohort (table 2). The percentage in the naïve cohort was 2.0%. No difference was found in the risk for SGA when metformin cohort was compared with naïve cohort in the main analyses (weighted OR (wOR) 0.97, 95% CI 0.75 to 1.37) or when the metformin-GDM subcohort was compared with naïve cohort in the additional analyses (wOR 1.01, 95% CI 0.75 to 1.37).

LGA was found in 4.0% of the children in the metformin cohort and 4.7% in the metformin-GDM subcohort (table 2). The percentage in the naïve cohort was 4.1%. No difference was found in the risk for LGA when metformin cohort was compared with the naïve cohort in the main analyses (wOR 0.91, 95% CI 0.75 to 1.11) but the risk was decreased in the metformin-GDM subcohort, in comparison to the naïve cohort, in the additional analyses (wOR 0.72, 95% CI 0.56 to 0.92).

**DISCUSSION**

No difference in LGA risk was found in the metformin cohort compared with the naïve cohort in the main analyses of this follow-up study to CLUE, but a decreased risk of LGA was found in the additional analyses with the metformin-GDM subcohort. A decreased risk of LGA birth for metformin versus insulin during pregnancy in this study cohort has already been described (online supplemental item 5). The recent large prospective clinical trial MiTy found a reduced risk of LGA in offspring of mothers with GDM exposed to non-pharmacological antidiabetic treatment. The naïve cohort has a 100% GDM rate, by definition, thus the number of outcomes and cohort size is the same for both the main analyses and additional analyses.

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**Table 2** Risk of being LGA or SGA at birth in the main analyses with metformin cohort and naïve cohort and in the additional analyses with metformin-GDM subcohort and naïve cohort

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Exposure</th>
<th>Metformin cohort</th>
<th>Naïve cohort</th>
<th>Unadjusted OR (95% CI)</th>
<th>IPTW-weighted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGA</td>
<td>Exposed to metformin cohort</td>
<td>3964</td>
<td>82675</td>
<td>92 (2.3)</td>
<td>1659 (2.0)</td>
</tr>
<tr>
<td>LGA</td>
<td>Exposed to metformin cohort</td>
<td>3964</td>
<td>82675</td>
<td>159 (4.0)</td>
<td>3415 (4.1)</td>
</tr>
</tbody>
</table>

*The numbers of outcomes represent counts in the main cohort before trimming of children outside the overlapping range of propensity scores.
†Naïve cohort refers to children of mothers with GDM exposed to non-pharmacological antidiabetic treatment. The naïve cohort has a 100% GDM rate, by definition, thus the number of outcomes and cohort size is the same for both the main analyses and additional analyses.
‡Covariates used in IPTW: mother’s age at delivery, calendar year of the childbirth, child's region of residency at birth, maternal comorbidities before pregnancy (pregestational T2DM and PCOS), maternal comorbidities during pregnancy (any toxemia in pregnancy, essential hypertension, gestational hypertension, pre-eclampsia), parity, educational level, maternal smoking during pregnancy, maternal prepregnancy BMI, gestational week of GDM diagnosis.
§Main analyses: cases with unknown outcome (3 in metformin cohort and 70 in naïve cohort) are not included in the denominator (%).
¶Additional analyses: cases with unknown outcome (0 in metformin-GDM subcohort and 70 in naïve cohort) are not included in the denominator (%).

GDM, gestational diabetes mellitus; IPTW, inverse probability of treatment weighting; LGA, large for gestational age; SGA, small for gestational age; T2DM, type 2 diabetes mellitus.
exposed to metformin+insulin compared with placebo+insulin in pregnant women with T2DM. Furthermore, a large meta-analysis found no change in LGA incidence between metformin-exposed and insulin-exposed neonates, with the caveat that the metformin groups in the underlying studies did not discriminate the use of additional insulin in the metformin treatment groups. In prospective clinical trials in obese non-diabetic women, metformin use versus placebo did not alter the risk of LGA birth, whereas in a recent cohort study on pregnant women without diabetes and PCOS exposed or non-exposed to metformin, a reduced LGA risk for metformin exposure was found. Prepregnancy BMI and gestational hyperglycemia are considered drivers of LGA risk in the offspring. In summary, current evidence suggests that metformin may reduce hyperglycemia-related LGA.

Our previous findings in the main CLUE study indicated a significantly increased risk of SGA associated with in utero exposure to metformin when compared with insulin (online supplemental item 5), but not for metformin+insulin versus insulin. The MiTy study found an overall shift towards lower birth weight and increased risk of SGA in offspring exposed to metformin+insulin compared with insulin+placebo in pregnant women with T2DM. Likewise, in a recent randomized double-blind study, metformin-exposed babies born to GDM mothers were born approximately 100 g lighter than those exposed to placebo.

A large meta-analysis found a significant decrease in birth weight after intrauterine exposure to metformin compared with insulin, but no difference in SGA risk. Other observational studies have also not found differences in SGA risk when comparing metformin and diet treatment among pregnant women with GDM. And indeed, no differences were found in this follow-up analysis to CLUE regarding SGA risk in the metformin cohort compared with the naïve cohort, neither in the main analysis nor with the narrowed metformin-GDM subcohort. Metformin crosses the placenta, and based on the findings above, it is discussed whether metformin affects feto-placental metabolism leading to a reduced birth weight and accelerated catch-up growth later in life.

However, large prospective studies in non-diabetic patient do not support a general impact of metformin on fetal weight; metformin did not alter median birthweight z score (percentile) placebo or SGA risk in non-diabetic obese pregnant women at doses of 1500–3000 mg/day. Birth weight and SGA risk were also not altered in babies born to women with gestational insulin resistance or PCOS.

Thus, it might be discussed that a potential (residual) lack of glucose control with insulin (or other comparator treatments) in GDM pregnancies leads to a relatively higher birth weight, for example, as suggested by better glycemic control with metformin versus placebo in MiTy. In the main CLUE study, the risk of SGA birth was increased for drug-naïve GDM women compared with those on insulin with wOR 0.72, 95% CI 0.56 to 0.92 (see online supplemental item 5), which could be indicative of insulin use shifting towards higher birth weight. As large prospective studies like EMERGE (NCT02980276) will be needed to clearly determine the underlying mechanisms, practitioners are well advised to monitor fetal growth and discontinue metformin in case of emerging growth restriction as well as counteracting overly fetal growth in utero in insulin-treated mothers.

Similar to the main CLUE study, this follow-up study has a number of strengths, being a comprehensive study involving national coverage of mothers’ exposure to metformin across the various levels of healthcare, allowing the results to be generalizable to the Finnish population. GDM in this study was identified from multiple sources (diagnosis code or laboratory records), which should provide extensive and precise information. Also, the use of IPTW methods based on PS, including a broad range of maternal characteristics, improved comparability between the cohorts and reduced the potential for confounding.

There were several limitations in this follow-up study that deserve comment. Drug exposure was potentially misclassified due to the non-use of the dispensed drug (eg, due to gastrointestinal side effects of metformin) and, subsequently, dose stratification was not possible. Confounding by severity could affect the results, since information on PCOS, T2DM and GDM severity was not available in the data. Although IPTW methods were used to account for broad range of characteristics (eg, demographic characteristics, maternal comorbidities, pregnancy-related variables), the prevalence of PCOS, T2DM and GDM differed across treatment cohorts, which potentially caused a residual confounding. While the metformin cohort had the highest proportion of PCOS and the lowest proportion of GDM, the naïve cohort included, by definition, women with GDM diagnosis only. Furthermore, 27% of the metformin cohort was trimmed when IPTW analysis was performed due to PS non-overlapping in the main analyses, likely due to the absence of GDM diagnosis during pregnancy (table 1). Only 0.5% of the metformin cohort was trimmed when the PS procedure was applied in the additional analyses with metformin-GDM subcohort. Therefore, the additional analyses with metformin-GDM subcohort and naïve cohort improved the generalizability and robustness of the results, since a smaller proportion of the children were trimmed.

CONCLUSION

In conclusion, this CLUE follow-up study supports previous findings that in utero exposure to metformin in comparison to drug-naïve GDM is not associated with an increased risk of SGA or LGA. The observed decrease in the risk of LGA in the analyses focusing on mothers with GDM may imply residual confounding. Regarding SGA risk, the results of this analysis, and even more the neutral outcomes of prospective studies in non-GDM
indications add to an unclear relationship between metformin exposure in utero and potential risk of lower birth weight, as seen versus insulin. For the time being, physicians are well advised to consider other treatment options than metformin when (risk of) intrauterine growth restriction is observed. Large prospective studies assessing metformin alone versus placebo in GDM pregnancies, like EMERGE (NCT02980276) will help to clear the sight.

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Contributors

KMGB developed the study idea, backbone and synopsis as the outcome of a cumulative assessment on the benefit/risk profile of metformin during pregnancy in 2016, in her role as Global Medical representative of the metformin originator Merck KGaA, Darmstadt, Germany and represented the company, which was the study sponsor and significantly contributed to the manuscript. She also acts as guarantor for this publication. JSc, CF and EB (all Merck KGaA, Darmstadt, Germany) contributed to finetuning the study concept, protocol development, data analysis and manuscript. The study was conducted by IQIVA, contracted by Merck KGaA, Darmstadt, Germany.

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Competing interests

KMGB, CF, EB and JSc are full-time employees of Merck KGaA, Darmstadt, Germany, the metformin originator and sponsor of this study, and participated in the authoring/revision of the manuscript. IQIVA performs commissioned pharmacoepidemiological studies, including this one, for several pharmaceutical companies. LS and RT are employees of IQIVA. JSO and KMH were employees of IQIVA at the time of conducting the study.

Patient consent for publication

Not applicable.

Ethics approval

The Ethics Committee of the Hospital District of Helsinki and Uusimaa, Finland, granted the CLUE study a favorable approval (reference number HUS/1742/2017). This study was a retrospective analysis, therefore, informed consent by participants was not required.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Data may be obtained from a third party and are not publicly available. All data relevant to the study are included in the article or uploaded as supplementary information.

Supplemental material

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