Non-Interventional Study Report

Title	Consequences for life of children with *in utero* exposure to metformin in Finland (CLUE)–a register-based cohort study
Study number	Merck study number: MS200084_0011 EPID Research: ER-9550
Version identifier of the final study report	Version 1.0
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EU PAS register number	EUPAS19686
Sponsor	Merck KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany
Coordinating Investigator/ Principal Investigator(s)	Pasi Korhonen PhD, Adj. Prof. Biostatistics, Senior Principal EPID Research Metsänneidonkuja 6, FI-02130 Espoo, Finland
Active substance	Metformin (A10BA02)
Medicinal product	Metformin, all single substance products with ATC code A10BA02
Product reference	EMR200084
Marketing authorization holder(s)	Merck Healthcare KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany
Joint PASS	No
Research question and objectives	To estimate the risk of long-term diagnoses long-term and diagnosis at birth in children with *in utero* exposure to metformin only, in children with *in utero* exposure to a combination of metformin and insulin, and in children born to mothers with GDM and naïve to *in utero* exposure to pharmacological antidiabetic treatment, as compared to children exposed *in utero* to insulin only.
Country of study	Finland
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Abstract

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Names and Affiliations of Coordinating Investigator/Principal Investigators:

Pasi Korhonen
PhD, Adj. Prof. Biostatistics, Senior Principal
EPID Research

Keywords:

Child health; Metformin; Pharmacoepidemiology; Pregnancy; Registries

Rationale and background:

Metformin is used during pregnancy outside of the approved indications to treat hyperglycemia in gestational diabetes mellitus (GDM), pre-gestational type 2 diabetes mellitus (PGDM2), and polycystic ovary syndrome (PCOS). The evidence regarding the long-term effects on the offspring remain scarce.

Research Question and Objectives:

Long-term and immediate effects of exposure to metformin *in utero* among the children of all pregnant women in Finland were investigated. The primary long-term outcomes were diagnoses of obesity, hypoglycemia, hyperglycemia, hypertension, diabetes mellitus, PCOS (girls only), and diagnoses related to challenges in motor-social development. Secondary outcomes were long-term growth-related outcomes and immediate outcomes.

Study Design:

This was a cohort study using Finnish population-based registers.

Setting:

The main study population included all children born between 1996 and 2016 in Finland. The children were divided into four cohorts based on treatment exposure during pregnancy: metformin (only metformin dispensed during pregnancy), combination (both metformin and insulin dispensed), insulin (only insulin dispensed), and naïve (children born to mothers with GDM, but neither metformin or insulin dispensed).

The children were followed from their birth until the end of 2016, death, or migration abroad, whichever occurred first. The maximum follow-up for the long-term effects was up to the age of 20 years.

Subjects and study size:

Eligible mothers fulfilled all inclusion criteria: singleton pregnancy resulting in live birth; record of GDM during the pregnancy and/or dispensation of metformin and/or insulin during the pregnancy; age between 18 and 45 years at delivery; and registered in Finland throughout the pregnancy.

Exclusion criteria for the mothers were: previously diagnosed or post-partum T1DM; dispensation of systemic glucocorticoids during pregnancy; or dispensation of antidiabetic medications other than metformin or insulin during pregnancy.

There were 4,052, 897, and 6,430 children in the metformin, combination, and insulin cohort, respectively, during the period of 1996-2016. The corresponding numbers during 2004-2016 were 3,967, 889, and 5,273 children. Further, the naïve cohort included 82,745 children during 2004-2016.

Variables and data sources:

The study database was constructed from the following Finnish data sources: Prescription register, Medical Birth Register, Register of Congenital Malformations, Care Register for Health Care , Register of Primary Health Care Visits, Population Register Centre, Statistics Finland, and regional laboratory databases.

The primary outcomes in the children were collected from the age of one week until the end of follow-up. Exposure during pregnancy was based on drug dispensations. The covariates included maternal variables (demographic factors, pregnancy-related variables, comorbidities during pregnancy, smoking, and dispensation of antidiabetic medications within three months before the pregnancy), and variables related to the child (year of birth and characteristics at birth).

Statistical Analysis:

The risk of each long-term effect was investigated as a time-to-event variable where the start time was at the age of one week. Unadjusted, covariate-adjusted, and propensity score (PS)-weighted Cox proportional hazards models were used. The insulin cohort was the reference group in all analyses.

Results:

The children born during 1996-2016 (n=11,379) are not reported separately, as the vast majority of them were born during 2004-2016 when the naïve cohort was also included (n=92,874).

No increased risk was found in the metformin cohort compared to the insulin cohort regarding the risk of developing long-term outcomes: obesity (PS-weighted HR 1.14, 95% confidence interval (CI) 0.83 to 1.55), hypoglycemia (PS-weighted HR 1.00, 95% CI 0.61 to 1.64), hyperglycemia (PS-weighted HR 1.23, 95% CI 0.63 to 2.42), diabetes mellitus (PS-weighted HR 1.19, 95% CI 0.51 to 2.82), and diagnoses related to challenges in motor-social development (PS-weighted HR 1.09, 95% CI 0.93 to 1.27). The low number of hypertension and PCOS diagnoses hindered performing comparative analyses for these outcomes, and the number of children developing diabetes mellitus was also low. The results were by large consistent when the combination cohort was compared to the insulin cohort.

While the risk of developing hypoglycemia, hyperglycemia, and diabetes mellitus in long-term follow-up was unaffected, the naïve cohort appeared less affected by obesity (PS-weighted HR 0.71, 95% CI 0.55 to 0.92) and diagnosis related to challenges in motor-social development (PS-weighted HR 0.88, 95% CI 0.78 to 0.98), compared to the insulin cohort.

Discussion and Conclusion:

This study did not show an increase in the long-term risk of obesity or diagnosis of motor-social challenges in children with *in utero* exposure to metformin (alone or in combination with insulin), compared with insulin exposure. Further, the risk of hypoglycemia and hyperglycemia after the age of one week seemed similar between these exposures. Since few cases of hypertension, diabetes mellitus, and PCOS were detected among children with *in utero* exposure to metformin, no conclusions can be drawn on the risk of these long-term outcomes.

The full study report will be published in the EU PAS Register® at latest one month after EMA endorsement of the full report.