Consequences for life of children with in utero exposure to metformin in Finland (CLUE) – a register-based cohort study

First published: 13/07/2017

Last updated: 02/07/2024

Study Finalised

Administrative details

EU PAS number

EUPAS19686

Study ID

47386

DARWIN EU® study

No

Study countries

Finland

Study description

Metformin is used during pregnancy to treat hyperglycaemia in gestational diabetes mellitus (GDM) and pre-gestational diabetes (PGDM), and to treat the polycystic ovary syndrome (PCOS). Despite the use of metformin during pregnancy in these three conditions, the long-term effects of metformin exposure in utero have not been widely studied in the children beyond two years of age. Evidence on these effects is of major interest, as metformin crosses the placenta and might therefore have long-term effect on the children. Using population-level data from Finland, this study will provide information on these long-term effects among children of women who used metformin during pregnancy. The aim of this study is to investigate the long-term and immediate effects of exposure to metformin in utero among the children of all pregnant women treated with metformin, regardless of the purpose of use. The long-term effects include e.g. diagnoses of obesity, hypo- and hyperglycaemia, diabetes mellitus, diagnoses related to challenges in motor-social development, and growth-related outcomes. In addition, immediate effects of exposure to metformin in utero will be investigated, including growth outcomes at birth, preterm birth, perinatal mortality, hypo- and hyperglycaemia at birth, and major congenital anomalies. The long-term effects described above in the children of women pregnant from 1996 onwards and treated during their pregnancy with metformin only, or with a combination of insulin and metformin, will be compared to the children of pregnant women treated during their pregnancy with insulin only. Additionally, and making use of the availability of GDM diagnosis data from 2004 onwards, a cohort of children born to mothers with GDM and naïve to in utero exposure to pharmacological antidiabetic treatment will be added for comparison.

Study status

Finalised

Research institutions and networks

Institutions

IQVIA

United Kingdom

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Institution | Non-Pharmaceutical company | ENCePP partner

Contact details

Study institution contact

Pasi Korhonen PAS_registrations@iqvia.com

Study contact

PAS_registrations@iqvia.com

Primary lead investigator

Massoud Toussi

Primary lead investigator

Study timelines

Date when funding contract was signed

Actual: 08/02/2017

Study start date

Planned: 05/11/2018

Actual: 30/11/2018

Data analysis start date

Planned: 31/12/2018

Actual: 30/11/2018

Date of final study report

Planned: 31/12/2020

Actual: 04/08/2020

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

Merck KGaA

Study protocol

ER-9550_Merck Metformin CLUE_protocol_1.0_2017-05-15_FINAL_CLEAN_signed.pdf (3.13 MB)

Regulatory

Was the study required by a regulatory body?

No

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

Disease /health condition

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Assessment of risk minimisation measure implementation or effectiveness

Data collection methods:

Secondary use of data

Main study objective:

The main objective is to estimate longitudinally the prevalence, incidence and risk of diagnoses (obesity, hypoglycaemia, hyperglycaemia, hypertension, diabetes mellitus, PCOS (girls only), and diagnoses related to challenges in motor-social development) from the age of one week for as long as data are available in the four cohorts of interest.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Anatomical Therapeutic Chemical (ATC) code

(A10A) INSULINS AND ANALOGUES

INSULINS AND ANALOGUES

(A10BA02) metformin

metformin

Medical condition to be studied

Gestational diabetes

Type 1 diabetes mellitus

Type 2 diabetes mellitus

Polycystic ovaries

Population studied

Short description of the study population

The study population of the children will be assembled using the following criteria relative to the mothers.

Inclusion criteria:

1. Singleton pregnancy resulting in live birth, recorded in the Medical Birth Register during the study inclusion period (1996-2016).

2. Record of GDM during the pregnancy, defined as a diagnosis of GDM recorded in the Medical Birth Register, HILMO or AvoHILMO, or a pathological OGTT in the Medical Birth Register, or dispensation of metformin and/or insulin

recorded in the Prescription register during the pregnancy, i.e. on the first day of the last menstrual period (LMP) or any time after it until the date of delivery.
3. Age between 18 and 45 years at delivery, recorded in the Medical Birth Register.
4. Registered in Finland throughout the pregnancy, based on the region of residency recorded in the Population Register Centre.

Exclusion criteria:
1. Previously diagnosed T1DM recorded in the Medical Birth Register, or post-partum T1DM defined as at least one record of a diagnosis code for T1DM in HILMO or AvoHILMO registers after delivery.
2. Dispensation of systemic glucocorticoids known to interfere with metformin or insulin recorded in the Prescription register during pregnancy, i.e. on the first day of the LMP or any time after it until the date of delivery.
3. Dispensation of antidiabetic medications other than metformin or insulin (e.g. acarbose, thiazolidinediones, sulphonylureas, glinides, or glucagon-like peptide 1 (GLP-1) agonists, recorded in the Prescription register during pregnancy, i.e. on the first day of the LMP or any time after it until the date of delivery.

Age groups

- Adolescents (12 to < 18 years)
- Children (2 to < 12 years)
- Infants and toddlers (28 days – 23 months)
- Preterm newborn infants (0 – 27 days)
- Term newborn infants (0 – 27 days)
- Adults (18 to < 46 years)
- Adults (46 to < 65 years)

Special population of interest

Pregnant women

Estimated number of subjects

64.300

Study design details

Outcomes

The primary outcomes are the long-term diagnoses collected from the age of one week for as long as data are available (maximum follow-up period 20 years). The secondary outcomes include the immediate effects at birth, up to one year of age and long-term growth-related effects (maximum follow-up period 16 years).

Data analysis plan

For the primary objectives, the prevalence and incidence of children having a long-term diagnosis of interest will be estimated with 95% confidence interval separately within each study cohort and in the total population. The cumulative risk of permanent outcomes will also be characterised using the Kaplan-Meier estimator. In the analyses, three different Cox proportional hazards models will be used: unadjusted, adjusted, and adjusted using also propensity scores. The same three models will be used in logistic regression models to compare the yearly prevalence of the permanent long-term effects. For the secondary objectives, similar analyses will be conducted as for the primary objectives, considering the nature of the outcome and whether the outcomes are immediate at birth or long-term. For continuous outcomes, linear regression analyses will be conducted. In all regression analyses, the children with in utero exposure to insulin only will be considered as the reference group.

Documents

Study results

ER-9550_Merck Metformin CLUE_NIS Report_Abstract for EU PAS Register_2020-08-04.pdf (381.49 KB)

Study, other information

Annex5_DoIForm_EPID Research_1_20170712.pdf (6.03 MB)

Annex5_DoIForm_EPID Research_2_20170712.pdf (7.24 MB)

Annex5_DoIForm_other investigators_20170712.pdf (1.95 MB)

Annex5_DoIForm_other investigators_revised_20170811.pdf (2.03 MB)

Study publications

Brand KM, Saarelainen L, Sonajalg J, Boutmy E, Foch C, Vääräsmäki M, Morin-Papu...

Brand KM, Thoren R, Sõnajalg J, Boutmy E, Foch C, Schlachter J, Hakkarainen KM,...

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

This study has been awarded the ENCePP seal

Conflicts of interest of investigators

Annex5_DoIForm_Pasi Korhonen.pdf (707.06 KB)

Composition of steering group and observers

ER-9550_no steering group_for ENCePP_20170713.pdf (59.09 KB)

Data sources

Data source(s), other

Drugs and Pregnancy Finland

Data sources (types)

Administrative healthcare records (e.g., claims)

Disease registry

Drug dispensing/prescription data

Electronic healthcare records (EHR)

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No