Drug transporter protein -mediated drug interactions during pregnancy and offspring outcome; with special emphasis on second-generation antipsychotics and SSRIs (PgP and BCRP interactions and pregnancy)

First published: 26/04/2016

Last updated: 31/01/2020

Study Finalised

Administrative details

EU PAS number

EUPAS13051

Study ID

33382

DARWIN EU® study

No

Study countries

Finland

Study description

Background. Drug transporter proteins play an important role in the bioavailability and toxicity of drugs. P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) are the two important efflux transporter proteins in the human placenta. It is not known if drug transporter protein -mediated drug interactions account for the possible teratogenicity of drugs or if such interactions can also predispose to neonatal drug toxicity.Objectives. To investigate if concomitant use of two or more drug transporter substrates or a substrate and an inhibitor during first trimester is associated with an increased risk of offspring major congenital malformations. Specifically, we will assess the risk of overall malformations in offspring of women using SGAs, and the risk of cardiac malformations in offspring of women using SSRIs or bupropion, and the risk of severe or prolonged neonatal adaptation problems.Methods. This is a population-based cohort study based on the Drugs and Pregnancy project database in Finland. Data are derived from national health registers: the Medical Birth Register, the Register on Induced Abortions, the Malformation Register and the Prescription Register and Special Refund Entitlement Register. Data in these registers have been collected during Jan 1st 1996 - Dec 31st 2011 and include all births (live and still births), pregnancy terminations due to major congenital malformation, and information on drug purchases during pregnancy and 3 months before pregnancy. To this database we will further link data on individual drugs and their relation (substrate, inhibitor) to P-gp and BCRP from the University of Washington Metabolism and Transport Drug Interaction Database (DIDB). Offspring of women with concomitant use of two or more drug transporter substrates, or a combination of a substrate and an inhibitor, are compared to offspring of women using only one drug transporter specific substrate, and to unexposed.

Study status

Finalised

Research institutions and networks

Institutions

Finnish Institute for Health and Welfare (THL)

Finland

First published: 01/02/2024

Last updated: 01/02/2024

Institution | Educational Institution | Laboratory/Research/Testing facility

Teratology Information Service, Helsinki (TIS Helsinki), HUSLAB

Finland

First published: 09/04/2010

Last updated: 16/08/2011

Institution | Outdated | Educational Institution | Hospital/Clinic/Other health care facility | ENCePP partner

Department of Clinical Pharmacology Helsinki University and Helsinki University Hospital

Contact details

Study institution contact

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Study contact

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Primary lead investigator

Heli Malm

Primary lead investigator

Study timelines

Date when funding contract was signed

Actual: 02/01/2015

Study start date

Planned: 31/08/2016

Actual: 19/11/2018

Data analysis start date

Planned: 30/11/2016

Date of interim report, if expected

Planned: 31/05/2017

Date of final study report

Planned: 30/05/2018

Actual: 10/12/2019

Sources of funding

- Other

More details on funding

Finnish Medical Agency, National Institute of Health and Welfare, Social Insurance Institution

Study protocol

Research protocol_APR_25_2016.pdf (401.08 KB)

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:

Human medicinal product

Disease /health condition

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:

To investigate if concomitant use of two or more drug transporter substrates or a substrate and an inhibitor during first trimester is associated with an increased risk of offspring major congenital malformations. Specifically, we will assess the risk of overall malformations in offspring of women using SGAs, and the risk of cardiac malformations in offspring of women using SSRIs or bupropion.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Study drug International non-proprietary name (INN) or common name

BUPROPION

Anatomical Therapeutic Chemical (ATC) code

(N05A) ANTIPSYCHOTICS

ANTIPSYCHOTICS

(N06AB) Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors

Medical condition to be studied

Congenital anomaly

Population studied

Short description of the study population

Women exposed one month before pregnancy or during the first trimester to P-gp/BCRP polytherapy; P-gp/BRCP monotherapy; non-P-gp/BCRP polytherapy, and unexposed.

Age groups

- Preterm newborn infants (0 – 27 days)
- Term newborn infants (0 – 27 days)

Special population of interest

Pregnant women

Estimated number of subjects

1000000

Study design details

Outcomes

Major congenital malformations and major cardiac malformations, according to EUROCAT coding (www.eurocat-network.eu). Neonatal outcomes: Apgar score <7, need for respirator treatment, need for treatment in neonatal (intensive) care unit, need for care outside home at the age of one week

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Data analysis plan

All data are anonymized and coded prior to statistical analysis. The prevalence of specific outcomes is compared between the different exposure groups of pregnant women and their offspring. Crude and adjusted odds ratios (cOR and aOR) and 95% confidence intervals (CI) were calculated. Statistical significance was set at a P value of less than 0.05. Univariate analyses are used to study demographic differences between the study cohorts. Univariate and logistic regression are used to calculate crude and adjusted odds ratios (cOR and aOR), and 95% confidence intervals (CI) and to assess the association between exposures during pregnancy and major congenital malformations and other perinatal outcomes. Covariates will be tested using a P -value of < 0.1 to detect associations with exposure and outcome. If associated with both exposure and outcome, the covariate will be included as a true confounder in the analysis.

Documents

Study results

Asiakirja1.pdf (5.24 KB)

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

H_MALM_Annex5_DoIForm.pdf (920.86 KB)

Composition of steering group and observers

ENCEPP_Clarification of steering group.pdf (17.49 KB)

Signed code of conduct

DECL_COMPLIANCE_with ENCePP CoC.pdf (83.84 KB)

Signed code of conduct checklist

Checlist_ENCePP_CoC_for ENCePP Studies.pdf (374.03 KB)

Signed checklist for study protocols

ENCePP_checklist_study_protocols.pdf (536.83 KB)

Data sources

Data source(s), other

Drugs and Pregnancy Finland

Data sources (types)

Administrative healthcare records (e.g., claims)

Drug dispensing/prescription data

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