Antipsychotics in pregnancy and the risk of adverse pregnancy outcomes - a nationwide study

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Study | Planned

Administrative details

PURI
https://redirect.ema.europa.eu/resource/1000000134

EU PAS number
EUPAS1000000134

Study ID
1000000134

DARWIN EU® study
No

Study countries
Norway

Study description
Maternal use of antipsychotics is increasing in recent years. Questions remain as to the risk of spontaneous abortion among women who use antipsychotics in early pregnancy, also due to the methodological challenges of studying spontaneous abortion as an outcome. Therefore, using a novel pregnancy algorithm that captures early non-live births, we aim to assess the association of second-generation antipsychotic use during pregnancy with spontaneous abortions. In addition, we will assess associations with the other maternal and pregnancy outcomes.
We will use Norwegian nationwide registry data, which consist of the Medical Birth Registry

of Norway (MBRN), linked to the Norwegian Prescription Database (NorPD) covering all dispensed medications to outpatients, the Norwegian control and payment of health reimbursements (KUHR) covering primary care contacts, and the Norwegian Patient Registry (NPR) covering secondary care contacts, through the maternal personal identification number. Identification of pregnancy episodes and outcomes will be done using the pregnancy algorithm developed by PharmaSafe research group at the University of Oslo.
The primary exposure group is defined as second-generation antipsychotics during early pregnancy. Several comparison groups will be employed: 1. Unexposed, diseased comparison group 2. First-generation antipsychotics during pregnancy (Active comparator), 3. Exposed to second-generation antipsychotics only prior to pregnancy (Discontinuer).
The primary outcome is defined as spontaneous abortions. We will estimate the hazard ratio with 95% CI with each comparator group, while controlling for measured confounders identified using Directed Acyclic Graphs.
In the secondary analysis, we will restrict to pregnancies identified in the MBRN. We will assess the outcomes: preterm birth, small-for-gestational age (SGA), low Apgar score, transfer to NICU, congenital malformations, caesarean section, gestational diabetes, and preeclampsia.

Study status
Planned

Research institution and networks

Institutions

Pharmacoepidemiology and Drug Safety Research Group (PharmaSafe), University of Oslo

Norway
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08/11/2016

Institution
Educational Institution
ENCePP partner

Contact details

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Study timelines

Date when funding contract was signed
Planned:
08/04/2024

Study start date
Planned:
01/05/2024

Data analysis start date
Planned:
01/05/2024

Date of final study report
Planned:
28/02/2025

Sources of funding

- Other public funding (e.g. hospital or university)

More details on funding

University of Oslo provided funds for data access and storage.
Dr. Sakai was funded International Alliance for PharmacoGenetic Epidemiology Excellence (iAPOGEE) visiting scholarship and Scandinavia-Japan Sasakawa Foundation for this project.

Study protocol

Antipsychotics in pregnancy and the risk of adverse pregnancy outcomes.pdf(3 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:
Human medicinal product

Study type:
Non-interventional study

Scope of the study:
Safety study (incl. comparative)

Data collection methods:
Secondary data collection

Study design:
Cohort study using nation-wide registry data.

Main study objective:
To evaluate the association of exposure to second-generation antipsychotics during pregnancy with the risk of spontaneous abortion.

Study Design

Non-interventional study design
Cohort

Study drug and medical condition

Name of medicine, other
First-generation antipsychotics, Second-generation antipsychotics

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Anatomical Therapeutic Chemical (ATC) code
(N05A) ANTIPSYCHOTICS
(N05AA01) chlorpromazine
(N05AA02) levomepromazine
(N05AA03) promazine
(N05AA04) acepromazine
(N05AA05) triflupromazine
(N05AA06) cyamemazine
(N05AA07) chlorproethazine
(N05AB01) dixyrazine
(N05AB02) fluphenazine
(N05AB03) perphenazine
(N05AB04) prochlorperazine
(N05AB05) thiopropazate
(N05AB06) trifluoperazine
(N05AB07) acetophenazine
(N05AB08) thioproperazine
(N05AB09) butaperazine
(N05AB10) perazine
(N05AC01) periciazine
(N05AC02) thioridazine
(N05AC03) mesoridazine
(N05AC04) pipotiazine
(N05AD01) haloperidol
(N05AD02) trifluperidol
(N05AD03) melperone
(N05AD04) moperone
(N05AD05) pipamperone
(N05AD06) bromperidol
(N05AD07) benperidol
(N05AD08) droperidol
(N05AD09) fluanisone
(N05AE01) oxypertine
(N05AE02) molindone
(N05AE03) sertindole
(N05AE04) ziprasidone
(N05AE05) lurasidone
(N05AF01) flupentixol
(N05AF02) clopenthixol
(N05AF03) chlorprothixene
(N05AF04) tiotixene
(N05AF05) zuclopenthixol
(N05AG01) fluspirilene

(N05AG02) pimozide
(N05AG03) penfluridol
(N05AH01) loxapine
(N05AH02) clozapine
(N05AH03) olanzapine
(N05AH04) quetiapine
(N05AH05) asenapine
(N05AH06) clotiapine
(N05AL01) sulpiride
(N05AL02) sultopride
(N05AL03) tiapride
(N05AL04) remoxipride
(N05AL05) amisulpride
(N05AL06) veralipride
(N05AL07) levosulpiride
(N05AX07) prothipendyl
(N05AX08) risperidone
(N05AX10) mosapramine
(N05AX11) zotepine
(N05AX12) aripiprazole
(N05AX13) paliperidone
(N05AX14) iloperidone
(N05AX15) cariprazine
(N05AX16) brexpiprazole

Medical condition to be studied
Schizophrenia
Bipolar disorder
Mania

Additional medical condition(s)
Depressive disorder with psychotic symptoms

Population studied

Short description of the study population
In the primary analysis, all pregnancies identified in the MBRN (Medical Birth Registry of Norway) for pregnancies lasting ?12 weeks, and primary and secondary care registries for pregnancies lasting <12 weeks. In the secondary analysis, we will restrict to pregnancies identified in the MBRN.

Age groups
Adults (18 to < 46 years)

Special population of interest
Pregnant women

Estimated number of subjects
860000

Study design details

Setting
We will use Norwegian nationwide registry data, which consist of the Medical Birth Registry of Norway (MBRN), linked to the Norwegian Prescription Database (NorPD) covering all dispensed medications to outpatients, the Norwegian control and payment of health reimbursements (KUHR) covering primary care contacts and the Norwegian Patient Registry (NPR) covering secondary care contacts through the maternal personal identification number.

Comparators
Several comparison groups will be employed: 1. Unexposed, diseased comparison group, 2. First-generation antipsychotics during pregnancy (Active comparator), 3. Exposed to second-generation antipsychotics only prior to pregnancy (Discontinuer).

Outcomes
The primary outcome is defined as spontaneous abortions. Elective termination is considered a competing outcome. The secondary outcomes are preterm birth, small-for-gestational-age (SGA), low Apgar score, transfer to NICU, congenital malformations, gestational diabetes, preeclampsia, caesarean section.

Data analysis plan
In the primary analysis, we will estimate the hazard ratio with 95% CI with each comparator group, while controlling for measured confounders identified using Directed Acyclic Graphs.

Data management

Data sources

Data source(s)
Norwegian Health Registers

Data source(s), other
Norwegian nationwide registry data, which consist of the Medical Birth Registry of Norway (MBRN), linked to the Norwegian Prescription Database (NorPD) covering all dispensed medications to outpatients, the Norwegian control and payment of health reimbursements (KUHR) covering primary care contacts and the Norwegian Patient Registry (NPR) covering secondary care contacts through the maternal personal identification number.

Data sources (types)
Drug dispensing/prescription data
Population registry
Pregnancy registry

Use of a Common Data Model (CDM)

CDM mapping
No

Data quality specifications

Check conformance
Yes

Check completeness
Yes

Check stability
Unknown

Check logical consistency
Yes

Data characterisation

Data characterisation conducted
Not applicable