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

First published: 02/05/2024

Last updated: 28/02/2025

Study Planned

Administrative details

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 institutions and networks

Institutions

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

Norway

First published: 19/10/2016

Last updated: 06/11/2025

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: 28/02/2026

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)

protocol_Antipsychotic medications_update250228.pdf (3.8 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 use of data

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

Medicinal product name, other

First-generation antipsychotics, Second-generation antipsychotics

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Anatomical Therapeutic Chemical (ATC) code

(N05A) ANTIPSYCHOTICS

ANTIPSYCHOTICS

(N05AA01) chlorpromazine

chlorpromazine

(N05AA02) levomepromazine

levomepromazine

(N05AA03) promazine

promazine

(N05AA04) acepromazine

acepromazine

(N05AA05) triflupromazine

triflupromazine

(N05AA06) cyamemazine

cyamemazine

(N05AA07) chlorproethazine

chlorproethazine

(N05AB01) dixyrazine

dixyrazine

(N05AB02) fluphenazine

fluphenazine

(N05AB03) perphenazine

perphenazine

(N05AB04) prochlorperazine

prochlorperazine

(N05AB05) thiopropazate

thiopropazate

(N05AB06) trifluoperazine

trifluoperazine

(N05AB07) acetophenazine

acetophenazine

(N05AB08) thioproperazine

thioproperazine

(N05AB09) butaperazine

butaperazine

(N05AB10) perazine

perazine

(N05AC01) periciazine

periciazine

(N05AC02) thioridazine

thioridazine

(N05AC03) mesoridazine

mesoridazine

(N05AC04) pipotiazine

pipotiazine

(N05AD01) haloperidol

haloperidol

(N05AD02) trifluperidol

trifluperidol

(N05AD03) melperone

melperone

(N05AD04) moperone

moperone

(N05AD05) pipamperone

pipamperone

(N05AD06) bromperidol

bromperidol

(N05AD07) benperidol

benperidol

(N05AD08) droperidol

droperidol

(N05AD09) fluanisone

fluanisone

(N05AE01) oxypertine

oxypertine

(N05AE02) molindone

molindone

(N05AE03) sertindole

sertindole

(N05AE04) ziprasidone

ziprasidone

(N05AE05) lurasidone

lurasidone

(N05AF01) flupentixol

flupentixol

(N05AF02) clopenthixol

clopenthixol

(N05AF03) chlorprothixene

chlorprothixene

(N05AF04) tiotixene

tiotixene

(N05AF05) zuclopenthixol

zuclopenthixol

(N05AG01) fluspirilene

fluspirilene

(N05AG02) pimozide

pimozide

(N05AG03) penfluridol

penfluridol

(N05AH01) loxapine

loxapine

(N05AH02) clozapine

clozapine

(N05AH03) olanzapine

olanzapine

(N05AH04) quetiapine

quetiapine

(N05AH05) asenapine

asenapine

(N05AH06) clotiapine

clotiapine

(N05AL01) sulpiride

sulpiride
(N05AL02) sultopride
sultopride
(N05AL03) tiapride
tiapride
(N05AL04) remoxipride
remoxipride
(N05AL05) amisulpride
amisulpride
(N05AL06) veralipride
veralipride
(N05AL07) levosulpiride
levosulpiride
(N05AX07) prothipendyl
prothipendyl
(N05AX08) risperidone
risperidone
(N05AX10) mosapramine
mosapramine
(N05AX11) zotepine
zotepine
(N05AX12) aripiprazole
aripiprazole
(N05AX13) paliperidone
paliperidone
(N05AX14) iloperidone
iloperidone
(N05AX15) cariprazine
cariprazine

(N05AX16) brexpiprazole

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

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.

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