Prenatal exposure to paracetamol and the risk of urogenital system disorders or neurodevelopmental disorders in offspring: a systematic review of observational studies

First published: 05/03/2020

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Study Finalised

Administrative details

EU PAS number

EUPAS33976

Study ID

33977

DARWIN EU® study

No

Study countries

☐ Netherlands

Study description

Evaluating the safety of medicines exposure during pregnancy involves several challenges, including confounding by indication, i.e. the event for which the medicine being prescribed may be directly associated with the outcome, and confounding by severity, i.e. women with more severe symptoms may be more likely to be exposed to the medicine, often at higher doses and for longer periods of time. The aim of this systematic review is to provide an overview of the available observational studies looking at the association between maternal paracetamol exposure during pregnancy and the risk of neurodevelopment disorders and urogenital system disorders in offspring. The review focuses on the methodology used in these observational studies and whether additional comparisons and reference groups have been used to evaluate the associations and the type of confounders that have been included in existing analyses. This approach follows that used in a recent publication assessing studies measuring the association between antidepressant exposure during pregnancy and risk of autism spectrum disorder and attention deficit hyperactivity disorder in offspring. The use of different comparator or reference groups in this publication provided supportive evidence examining whether statistically significant associations observed comparing risk in exposed women to risk in all unexposed women subject to confounding by indication was more or less likely to be causal 1.This review aims to provide some insight to whether the existing studies provide sufficient information to help determine whether the associations between maternal paracetamol exposure during pregnancy and the risk of neurodevelopment disorders and urogenital system disorders in offspring are likely to be causal, and to help make recommendations for or how to potentially address these challenges in further studies.

Study status

Finalised

Research institutions and networks

Institutions

European Medicines Agency (EMA)

First published: 01/02/2024

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Institution

Contact details

Study institution contact

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Primary lead investigator

Daniel Zondag

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 01/03/2018

Actual: 01/03/2018

Study start date

Planned: 02/04/2018

Actual: 02/04/2018

Data analysis start date

Planned: 03/04/2018

Actual: 03/04/2018

Date of final study report

Planned: 04/06/2018

Actual: 04/06/2018

Sources of funding

- EMA

Regulatory

Was the study required by a regulatory body?

Yes

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:

The aim of this systematic review is to provide an overview of the available observational studies looking at the association between maternal paracetamol exposure during pregnancy and the risk of neurodevelopment disorders and urogenital system disorders in offspring.

Study Design

Non-interventional study design

Systematic review and meta-analysis

Study drug and medical condition

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

PARACETAMOL

Medical condition to be studied

Cryptorchism

Hypospadias

Attention deficit hyperactivity disorder

Autism spectrum disorder

Additional medical condition(s)

Urogenital system disorders: cryptorchidism, late descent, anogenital distance (AGD) and other genital development outcomes such as penile length, penile width, testicular descent distance and hypospadia.Neurodevelopmental disorders: due to the different rating scales used, the outcomes of interest were broadly grouped into motor problems, behavioural problems, temperament problems, ADHD, ASD

Population studied

Short description of the study population

Pregnant women who had paracetamol exposure during pregnancy.

Age groups

- Adults (18 to < 46 years)
- Adults (46 to < 65 years)
- Adults (65 to < 75 years)

Special population of interest

Pregnant women

Estimated number of subjects

700000

Study design details

Outcomes

Urogenital system disorders: cryptorchidism, late descent, anogenital distance (AGD) and other genital development outcomes such as penile length, penile width, testicular descent distance and hypospadia.Neurodevelopmental disorders: due to the different rating scales used, the outcomes of interest were broadly grouped into motor problems, behavioural problems, temperament problems, ADHD, ASD

Data analysis plan

The interpretation of studies was based upon distinguishing between different comparisons and reference groups reported for the included observational studies. The rationale for this approach is that, for associations where a potential confounding by indication might affect the evaluation, assessment of causality may be better informed by assessing associations from different comparison/reference groups and study designs.

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 sources (types)

Other

Data sources (types), other

Prospective patient-based data collection, Case-control surveillance database

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