Pregnancy outcome after rheumatologic methotrexate (MTX) treatment prior to or during early pregnancy: a prospective multicenter cohort study (Rheumatologic MTX treatment and pregnancy outcome)

First published: 25/04/2012 Last updated: 01/04/2024





# Administrative details

| EU PAS number    |  |  |
|------------------|--|--|
| EUPAS2566        |  |  |
| Study ID         |  |  |
| 28099            |  |  |
| DARWIN EU® study |  |  |
| No               |  |  |
| Study countries  |  |  |
| Canada           |  |  |
| Finland          |  |  |

| France        |  |  |
|---------------|--|--|
| Germany       |  |  |
| Israel        |  |  |
| Italy         |  |  |
| Netherlands   |  |  |
| Switzerland   |  |  |
| United States |  |  |

#### Study description

Methotrexate (MTX) is known as a teratogen that causes a specific embryopathy. This is based on several retrospective case reports (e.g. Seidahmed 2006, Yedlinski 2005, Adam 2003, Chapa 2003, Krähenmann 2002, Wheeler 2002, Bawle 1998, and Milunsky 1968.). MTX has been used as an abortifacient, in cancer therapy, and beginning in the 90th for rheumatoid arthritis and some autoimmune diseases. The dose of MTX varies depending on the treatment indication and is lower in rheumatic diseases. There is still uncertainty concerning the risk of low-dose methotrexate therapy during pregnancy. As there is only one small prospective study, which observed no major birth defects in 28 pregnancies (Lewden 2004), no precise risk evaluation can be made so far. Furthermore, it has been debated how long prior to conception MTX therapy should be stopped. Recently, a broad international panel of rheumatologists recommended stopping MTX at least 3 months before conception (Visser 2009). Study Target: To assess the risk of low-dose MTX exposure in early pregnancy. Primary Outcome: Rate of major birth defects, rate of specific MTX embryopathy (time frame up to approximately 8 weeks after birth), rate of spontaneous abortion, intrauterine growth retardation (IUGR) in malformed and non malformed newborns (criterion: birth weigth), rate of prematurity. There are three prospectively ascertained groups to be compared:1) Exposed group with maternal exposure of low-dose MTX for rheumatic/autoimmune diseases, 2) Control group 1 ("disease group"):

Pregnant women with rheumatic /autoimmune diseases without MTX during pregnancy, 3) Non-exposed control group 2 ("general control"): No MTX, no rheumatic / autoimmune diseases.

## **Study status**

Finalised

# Research institutions and networks

## Institutions

| Pharmakovigilanzzentrum Embryonaltoxikologie (Embryotox Berlin), Charité-Universitätsmedizin |  |  |
|--|--|--|
| Germany  |  |  |
| First published: 22/02/2010  |  |  |
| <b>Last updated:</b> 30/12/2013  |  |  |
| Institution Outdated Educational Institution ENCePP partner                                  |  |  |

## **Networks**

| European Network of Teratology Information Services (ENTIS) |
|---|
| Austria   |
| Czechia   |
| Finland   |
| France  |

| Germany                         |
|---------------------------------|
| Greece                          |
| Italy                           |
| ☐ Netherlands                   |
| Spain                           |
| Switzerland                     |
| United Kingdom                  |
| First published: 31/05/2010     |
| <b>Last updated:</b> 13/05/2024 |
| Network ENCePP partner          |

## Contact details

## **Study institution contact**

Christof Schaefer christof.schaefer@charite.de

Study contact

christof.schaefer@charite.de

## **Primary lead investigator**

Corinna Weber-Schoendorfer

**Primary lead investigator** 

# Study timelines

Date when funding contract was signed

Actual: 06/02/2012

#### Study start date

Actual: 06/02/2012

#### Data analysis start date

Actual: 09/08/2012

#### **Date of final study report**

Planned: 31/12/2012 Actual: 21/12/2012

# Sources of funding

Other

## More details on funding

Bundesministerium für Gesundheit, Senatsverwaltung Berlin

# Study protocol

Arthritis Rheumatol\_abstract.pdf (145.4 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 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:**

Primary data collection

#### Main study objective:

To assess the risk of low-dose methotrexate (MTX) exposure in early pregnancy.

# Study Design

### Non-interventional study design

Cohort

# Study drug and medical condition

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

# Population studied

#### Short description of the study population

Women on MTX (≤30mg/week) either in the post-conception period or within 12 weeks before conception.

#### Age groups

Preterm newborn infants (0 - 27 days)

Term newborn infants (0 - 27 days)

Infants and toddlers (28 days - 23 months)

Adults (18 to < 46 years)

Adults (46 to < 65 years)

#### Special population of interest

Pregnant women

#### **Estimated number of subjects**

1450

# Study design details

#### **Outcomes**

Rate of major birth defects, rate of specific MTX embryopathy, rate of spontaneous abortion, rate of elective terminations of pregnancies, birth weight, rate of prematurity, Definition of a "teratogenic time window", Evaluation of teratogenic dose-effect relationship.

#### Data analysis plan

Birth defect rates include live births and anomalies in elective terminations of pregnancies (ETOPs) and miscarriages. For calculating rates ofmajor birth defects possibly associated with a teratogen, welldefinedgenetic syndromes are excluded. See: Schaefer C, Ornoy A, Clementi M, Meister R, Weber-

Schoendorfer C. Using observational cohort data for studying drug effects on pregnancy outcome--methodological considerations. Reprod Toxicol. 2008,26:36-41. For calculation spontaneous abortion rate see Meister R, Schaefer C. Statistical methods for estimating the probability of spontaneous abortion in observational studies--analyzing pregnancies exposed to coumarin derivatives. Reprod Toxicol. 2008,26:31-5

### **Documents**

#### **Study publications**

Weber-Schoendorfer C, Chambers C, Wacker E, Beghin D, Bernard N, Network ofFren...

# 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

ENTIS provides drug risk assessment for pregnant patients and/or physicians. Exposed pregnancies are documented and after the expected date of delivery, follow-up is conducted both using a structured questionnaire or phone interview.

## 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**

Unknown