Effects of maternal modafinil treatment on fetal development and neonatal growth parameters - a multicenter case series of the European Network of Teratology Information Services (ENTIS)

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Last updated: 07/09/2026

Study Finalised

Administrative details

EU PAS number

EUPAS1000001106

Study ID

1000001106

DARWIN EU® study

No

Study countries

Australia

France

Germany
Israel
Italy
Japan
Netherlands
Spain
Switzerland
Türkiye
United Kingdom
United States

Study description

In recent years, safety concerns about modafinil exposure during pregnancy have emerged. In particular, increased risks for major congenital anomalies (MCA) and impaired fetal growth were reported, although study results were conflicting. Our investigation aims to examine previously reported safety signals.

Multicenter case series based on data from 18 Teratology Information Services from 12 countries. Modafinil exposed pregnancies with an estimated date of birth before August 2019 were included in this study. For prospectively ascertained pregnancies, cumulative incidences of pregnancy outcomes, rate of nonchromosomal MCA in first trimester exposed pregnancies and percentiles of neonatal/infant weight and head circumference (HC) were calculated. Potential dose-dependent effects on fetal growth were explored by linear regression models. Retrospectively ascertained cases were screened for pattern of MCA and other adverse events.

Study status

Finalised

Research institutions and networks

Institutions

Pharmakovigilanz- und Beratungszentrum für Embryonaltoxikologie (Embryotox), Charité-Universitätsmedizin, Berlin

Germany

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Institution | Educational Institution | ENCePP partner

Swiss Teratogen Information Service

First published: 01/02/2024

Last updated: 01/02/2024

Institution

University of California

First published: 01/02/2024

Last updated: 01/02/2024

Institution

MotherSafe, Sidney (Australia)

French Network of Pharmacovigilance Centers, Terappel (France)

Centre de Référence sur les Agents Tératogènes, Paris (France)

The Israeli Teratology Information Service, Jerusalem (Israel)

Italy

Centro di Riferimento Regionale di Tossicologia Perinatale, Firenze (Italy)

Teratology Information Service, Telefono Rosso, Catholic University of Sacred Heart, Rome (Italy)

TIS PADUA-CEPIG, Clinical Genetics Unit, Department of Women’s and Children’s Health, University of Padua (Italy)

Japan Drug Information Institute in Pregnancy (JDIIP), Tokyo (Japan)

Teratology Information Service of the Netherlands Pharmacovigilance Centre Lareb (Netherlands)

Clinical Pharmacology Service, Vall d'Hebron Hospital Universitari, Vall d'Hebron Barcelona Hospital Campus, TIS Barcelona (Spain)

Servicio de Información Telefónica sobre Teratógenos Español (SITTE) – Service for health professionals, Madrid (Spain)

Turkey

Medical Pharmacology Outpatient Clinics, Marmara University Education and Research Hospital, Istanbul

Terafar – Izmir Katip Celebi University Teratology Information, Training and Research Center, Izmir

Trabzon-TIS — Teratology Information Service, Department of Pharmacology, Karadeniz Technical University, Trabzon (Türkiye)

UK Teratology Information Service, Newcastle upon Tyne (UK)

Networks

European Network of Teratology Information Services (ENTIS)

- Austria
- Czechia
- Finland
- France
- Germany
- Greece
- Ireland
- Italy
- Netherlands
- Spain
- Switzerland
- United Kingdom

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Network **ENCePP partner**

Contact details

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Study contact

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Primary lead investigator

Marlies Onken

Primary lead investigator

Study timelines

Date when funding contract was signed
Planned: 13/12/2019

Actual: 13/12/2019

Study start date
Planned: 31/08/2019

Actual: 31/08/2019

Date of final study report
Planned: 19/12/2023

Actual: 19/12/2023

Sources of funding

More details on funding

The Berlin Embryotox Center of Clinical Teratology and Drug Safety in Pregnancy is financially supported by the German Federal Institute for Drugs and Medical Devices (BfArM); included German study cases were obtained from the Embryotox cohort. The UK Teratology Information Service is funded by the UK Health Security Agency. The Dutch Teratology Information Service is funded by the Ministerie van Volksgezondheid, Welzijn en Sport Research Unit on Congenital Anomalies-UIAC & Spanish Teratology Information Services SITTE and SITE are financially supported by Instituto de Salud Carlos III, Ministerio de Ciencia e Innovación, of Spain.

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:

Combined primary data collection and secondary use of data

Study design:

Multicenter case series

Main study objective:

In recent years, safety concerns about modafinil exposure during pregnancy have emerged. In particular, increased risks for major congenital anomalies (MCA) and impaired fetal growth were reported, although study results were conflicting. Our investigation aims to examine previously reported safety signals.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Medicinal product name

MODAFINIL

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

MODAFINIL

Anatomical Therapeutic Chemical (ATC) code

(N06BA07) modafinil

modafinil

Medical condition to be studied

Live birth

Abortion spontaneous

Abortion induced

Stillbirth

Congenital anomaly

Population studied

Short description of the study population

Modafinil exposed pregnancies with an estimated date of birth before August 2019 were included in this study. For prospectively ascertained pregnancies, cumulative incidences of pregnancy outcomes, rate of nonchromosomal MCA in first trimester exposed pregnancies and percentiles of neonatal/infant weight and head circumference (HC) were calculated. Potential dose-dependent effects on fetal growth were explored by linear regression models. Retrospectively ascertained cases were screened for pattern of MCA and other adverse events.

Special population of interest

Pregnant women

Study design details

Setting

18 Teratology Information Services from 12 countries.

Outcomes

One hundred and seventy-five prospectively ascertained cases were included, of which 173 were exposed at least during the first trimester. Cumulative incidences for live birth, spontaneous abortion and elective termination of pregnancy were 76.9% (95% CI, 68.0%-84.8%), 9.3% (95% CI, 5.0%-16.9%), and 13.9% (95% CI, 8.1%-23.1%), respectively. Nonchromosomal MCA was present in 3/150 live births, corresponding to an MCA rate of 2.0% (95%CI, 0.6%-6.1%), none were reported in pregnancy losses. Compared to reference standards, birth weight (BW) tended to be lower and neonatal HC to be smaller in exposed newborns (data available for 144 and 73 of 153 live births, respectively). In nonadjusted linear regression models, each 100 mg increase of average dosage per pregnancy day was associated with a decrease in standard

deviation score (SDS) of -0.28 SDS (95% CI, -0.45 to -0.10) for BW and of -0.28 SDS (95% CI, -0.56 to 0.01) for HC. Screening of 22 retrospectively reported cases did not reveal any specific pattern of MCA or other adverse outcomes.

Data analysis plan

For prospectively ascertained pregnancies, cumulative incidences of pregnancy outcomes, rate of nonchromosomal MCA in first trimester exposed pregnancies and percentiles of neonatal/infant weight and head circumference (HC) were calculated. Potential dose-dependent effects on fetal growth were explored by linear regression models. Retrospectively ascertained cases were screened for pattern of MCA and other adverse events.

Summary results

The results do not indicate an increased risk of MCA after in utero exposure to modafinil, but a tendency toward lower BW and reduced neonatal HC. However, these findings should be regarded as preliminary. Until further studies allow for a definite conclusion, modafinil should not be used during pregnancy.

Documents

Study publications

https://doi.org/10.1111/acps.13643

Data management

Data sources

Data sources (types)

Electronic healthcare records (EHR)

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