PASS information

Title	Butoconazole use in pregnancy: population-based case-control studies on adverse pregnancy outcomes in Hungary (study protocol RGD-77425).
Protocol version identifier	Final version
Date of last version of protocol	08 July 2013.
EU PAS register number	{Registration number}
Active substance	butoconazole (test drug) clotrimazole, miconazole, nystatin, metronidazole (therapeutic controls)
Medicinal product	all approved products in Hungary containing the above active substances
Product reference	the relevant gynecology products are not centrally authorized.
Procedure number	not applicable (MAH initiated study)
Marketing authorisation holder(s)	Gedeon Richter Plc.
Joint PASS	No
Research question and objectives	The primary objective is to evaluate butoconazole treatment as a potential risk factor for teratogenicity and/or spontaneous abortion in a population-based retrospective study in Hungary, based on National Health Insurance Fund Administration Database (OEP database) records. Secondary objectives: to evaluate therapeutic controls as risk factors in the same analyses, for comparative purposes. To collect epidemiologic data on all outcomes of butoconazole exposed pregnancies.
Country(-ies) of study	Hungary
Principal investigator	Dr. Nándor Ács Second Department of Obstetrics and Gynecology, Semmelweis University, School of Medicine, Budapest, Hungary

Marketing authorisation holder(s):

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2. List of abbreviations

95% CI	95% confidence interval
ATC	Anatomical Therapeutic Chemical classification system
BNO	the Hungarian adaptation of the ICD classification system
CA	congenital anomaly
GYEMSZI	National Institute for Quality- and Organizational Development in Healthcare and Medicines
GYEMSZI-OGYI	National Institute for Quality- and Organizational Development in Healthcare and Medicines- National Institute of Pharmacy
HCAR/ HCCSCA	Hungarian Congenital Abnormality Registry / Hungarian Case-Control Surveillance of Congenital Abnormalities databases
ICD	International Classification of Diseases
LMP	last menstrual period
NHIF	National Health Insurance Fund
NIHD /OEFI	National Institute for Health Development / Országos Egészségfejlesztési Intézet
OENO	Hungarian classification system for medical interventions in inpatients and outpatients
OEP	National Health Insurance Fund (Hungarian abbreviation)
OEP database	National Health Insurance Fund Administration Database
OGYI	National Institute of Pharmacy
PASS	Post-authorization safety study
Rx	drug prescription
SD	standard deviation
TAJ Number	social security identification number (a unique, 9-digit identification number for each insured person at the National Health Insurance Fund in Hungary)

3. Responsible parties

The study is planned as a scientific collaboration of Gedeon Richter Plc (MAH of a butoconazole product in Hungary), RxTarget Kft (contract research organiser in the field of OEP data request and analysis), the National Institute for Health Development (responsible for the HCAR / HCCSCA databases), together with clinical experts Nándor Ács MD, PhD, med habil (Principal Investigator), and Zoltán Kaló MSc PhD (consultant expert). Key responsibilities of the involved parties are tabulated below, and a more detailed description is provided in the main text of the protocol (Section 9).

Name	Address	Responsibilities	Contact person
Gedeon Richter Plc.	19-21 Gyömrői út, 1103 Budapest, Hungary	Study sponsorship, study planning and financing, project management.	János G. Pitter MD, PhD Head of Medical Strategy and Coordination Department, Gedeon Richter Plc. 32 Gyömrői út, Budapest 1103, Hungary. phone: +36 1 432 6418 email: j.pitter@richter.hu
RxTarget Kft.	9 Gulácsi Lajos u. 5008 Szolnok, Hungary	Participation in study planning and reporting, programming data analysis, OEP orrespondence.	György Rokszin MD. CEO, RxTarget Ltd. 9 Gulácsi Lajos utca, Szolnok 5008, Hungary phone: +36-70-372-1201 email: rokszin.gyorgy@rxtarget.hu
National Institute for Health Development (HCAR / HCCSCA databases)	2 Nagyvárad tér 1096 Budapest, Hungary	participation in study planning, and in drawing conclusions in the final report.	Csáky-Szunyogh Melinda Head of the Hungarian Congenital Abnormality Registry, National Institute for Health Development, 2 Nagyvárad tér, 1096 Budapest, Hungary phone: +36-1-4288-229 email: csszunyogh.melinda@oefi.antsz.hu
Nándor Ács MD, PhD, med. habil.	78/A Üllői út, 1082 Budapest, Hungary	Principal Investigator Consultant Expert in Gynecology. Participation in study planning and in drawing conclusions in the final report.	Nándor Ács MD Second Department of Obstetrics and Gynecology, School of Medicine, Semmelweis University 78/A Üllői út, 1082 Budapest, Hungary
Zoltán Kaló MD, MSc, PhD	ELTE Társdadalomtudományi Kar, H-1518 Budapest, Pf. 32	Consultant Expert in clinical research. Participation in study planning, and in drawing conclusions in the final report.	Zoltán Kaló MD, MSc, PhD Eötvös Lóránd University, Institute of Economics, Health Economics Research Centre Building B, 1/A Pázmány Péter sétány, 1117 Budapest, Hungary

4. Abstract

Butoconazole use in pregnancy: population-based case-control studies on adverse pregnancy outcomes in Hungary (study protocol No. 77425)

Rationale and background: Vaginal yeast carriage is frequently occurring in pregnancy. Pharmacotherapy of genital fungal infections during pregnancy may prevent against preterm birth. However, pharmacotherapy itself may pose a risk to the developing foetus (increased risk of spontaneous abortions or foetal defects / congenital anomalies). Butoconazole belongs to a therapeutic class which contains drugs considered safe in pregnancy, as well as drugs which must be avoided in pregnancy. Although butoconazole is administered locally, small amounts of the drug were shown to be adsorbed from the vaginal mucosa. The available non-clinical and clinical data on butoconazole safety in pregnancy is not conclusive. As butoconazole is on the market in Hungary from 2004, the available records in the relevant medical databases allow for a retrospective, large-scale analysis of the risk of adverse pregnancy outcomes in butoconazole exposed pregnant women.

Research question and objectives: The primary objective is to evaluate butoconazole treatment as a potential risk factor for teratogenicity and/or spontaneous abortion in a population-based database analysis study in Hungary, based on National Health Insurance Fund Administration Database (OEP database) records. Secondary objectives: to evaluate therapeutic controls (clotrimazole, miconazole, nystatin, metronidazole) as risk factors in the same analyses, for comparative purposes; and to collect epidemiologic data on all outcomes of butoconazole exposed pregnancies.

Study design: a population-based database analysis of all reported pregnancy outcomes, with case-control studies on the risk of spontaneous abortion and teratogenicity.

Population: all reported pregnancy outcomes reported to the OEP database from 01 January 2005 to 31 December 2011, excluding pregnancies without sufficient identification data of live birth offspring. Cases exposed to other drugs / other risk factors are not excluded from the study. Instead, a range of potential confounding factors is included in the statistical models.

Variables: The investigated pregnancy outcomes include ectopic pregnancy; spontaneous abortion; elective termination (foetal defects); elective termination (no foetal defects or unknown); stillbirth with foetal defects; stillbirth without foetal defects; live birth with congenital anomaly; live birth without congenital anomaly. Drug exposure time periods include the following time periods: Before conception; First trimester; After first trimester; During all pregnancy; Unknown. For the analysis of teratogenic effects, separate analyses for the 1st month, 2nd month, 3rd month, 2nd + 3rd month are also included.

Data sources: OEP database records.

Study size: based on national birth statistics, the OEP database is expected to contain about 1 100 000 pregnancy outcomes in the relevant time period (including about 670 000 live births).

Data analysis: logistic regression models for the case-control studies on spontaneous abortion and teratogenicity risk. Descriptive statistics for all types of pregnancy outcomes.

Milestones: Final protocol submission to GYEMSZI-OGYI for study approval is planned for June 2013. Final report of study results is planned to be finalized in January 2014.

5. Amendments and updates

Not applicable at present.

Future protocol amendments (if any) will be indicated in the table below.

Number	Date	Section of study protocol	Amendment or update	Reason
1	[date]	[text]	[text]	[text]
2				
3				
4				
...				

6. Milestones

Milestone	**Planned date**
Final study protocol	8 July 2013
Submission for GYEMSZI-OGYI approval	10 July 2013
Registration in the EU PAS Register	10 July 2013
Expected date of GYEMSZI-OGYI approval	9 September 2013
Start of data collection (OEP)*	10 September 2013
End of data collection (OEP)*	30 October 2013
Start of data analysis and statistics	1 November 2013
End of data analysis and statistics	15 January 2013
Final report of study results	15 March 2014

*: start and stop date of secondary use of existing data (database research).

7. Rationale and background

The hormonal milieu of pregnancy creates a suitable environment predisposing for the vulvovaginal colonisation of Candida. Vaginal yeast carriage is thus more frequent in pregnancy and increases with increasing periods of gestation [Weisberg M, 1986].

Pharmacotherapy of genital fungal infections during pregnancy (especially in the first trimester) was shown to have a preventive effect against preterm birth in the case of clotrimazole, while the limitations of the dataset did not allow the appropriate evaluation of other antifungal drugs [Czeizel AE, 2007].

When treating fungal infections in a pregnant woman, it is very important to select an antifungal agent that, whilst effectively treating the mother, will pose no risk to the developing foetus. Given the multitude of topical azoles available for the treatment of Candida vaginitis, it would seem reasonable to prefer locally applied products instead of the use of systemic antifungals if possible, especially in pregnancy. However, the potential risk of locally applied products can not be excluded since small amounts of imidazoles are absorbed from the human vagina [Fromtling RA, 1988; Rosa FW, 1987].

Gedeon Richter Plc is the MAH of Gynazol-1, a locally applied butoconazole containing product approved for the treatment of Candida vaginitis. The available non-clinical and clinical data regarding the safety of butoconazole in pregnancy is summarized below.

Non-clinical reproductive toxicity data on butoconazole

Butoconazole nitrate was not mutagenic when tested on microbial indicator organisms. No impairment of fertility was seen in rabbits or rats administered butoconazole nitrate in oral doses up to 30 mg/kg/day or 100 mg/kg/day respectively.

In pregnant rats administered 6 mg/kg/day (3-7 times the human dose, representing a 130- to 353-fold safety margin based on systemic serum levels) butoconazole nitrate intravaginally during the period of organogenesis, there was an increase in resorption rate and decrease in litter size, but no teratogenicity.

Butoconazole nitrate had no apparent adverse effect when administered orally to pregnant rats throughout organogenesis, at dose levels up to 50 mg/kg/day (5 times the human dose based on mg/m2). Daily oral doses of 100, 200, 300 or 750 mg/kg/day (10, 30 or 75 times the human dose based on mg/m2, respectively) resulted in foetal malformations (abdominal wall defects, cleft palate), but maternal stress was evident at these higher dose levels [FDA Label Information, 2003].

There were no adverse effects on litters of rabbits receiving butoconazole nitrate orally, even at maternally stressful dose levels (e. g. 150 mg/kg, 24 times the human dose based on mg/m2).

Butoconazole nitrate, like other azole antifungal agents, causes dystocia (abnormal or difficult childbirth) in rats when treatment is extended through parturition. However, this effect was not apparent in rabbits treated with as much as 100 mg/kg/day orally (16 times the human dose based on mg/m2).

In summary, the available non-clinical data raised the concern of adverse effects of butoconazole on human reproduction. According to the assessment of this issue by Gedeon Richter's Toxicology Research Department, the concern is modulated by the following factors:

Factors of increased concern in non-clinical studies	**Factors of decreased concern in non-clinical studies**
- malformations occurred; - effects on more than one stages of reproductive cycle (embriotoxicity, teratogenicity, childbirth complications); - maternal toxicity at teratogenic doses was limited to body weight decrease (a direct effect on foetus can not be excluded); - dose-related effects; - embriotoxic dose in rats < 10x human dose (based on mg/m2 calculations); - class alert (other molecules with similar structure and pharmacodynamics was shown to be teratogenic in animals, and human malformations were also reported, e.g. fluconazole).	- positive findings in rat vs. no signal in rabbit; - the observed malformations in rat (abdominal wall defects, cleft palate) do not reflect a common biological mechanism; - embriotoxic dose in rat at about 130- to 353-fold human dose (based on systemic serum levels).

Clinical data on butoconazole in pregnancy

In the pivotal efficacy trials with Gynazol 20 mg/g vaginal cream, 8 unexpected pregnancies occurred (< 1% of 911 enrolled patients), despite investigators' effort to exclude pregnant patients. Only 2 of the 8 women used Gynazol 20 mg/g vaginal cream; both patients carried the pregnancies to term without complications and delivered normal neonates. An additional 2 women received different formulations of sustained release butoconazole vaginal cream for 3 days; 1 of these women delivered a healthy baby, the other elected therapeutic abortion for an unwanted pregnancy. The remaining 4 women received other antifungal imidazoles without any complications.

In a clinical study (IND 17658) 200 pregnant women received butoconazole nitrate intravaginally for 3 or 6 days during the second and third trimesters. It has not been shown that butoconazole causes adverse effects on the foetus. Follow-up reports on infants born to these women have not shown that butoconazole causes any adverse effects [Richter Gedeon Plc., 2012].

In a surveillance clinical study of Michigan Medicaid recipients involving 229,101 completed pregnancies conducted between 1985 and 1992, 444 newborns had been exposed to vaginal butoconazole during the first trimester. A total of 16 (3.6%) major birth defects were observed (17 expected). Specific data were available for six defect categories, including (observed/expected) 4/4 cardiovascular defects, 1/1 limb reduction defects, and 0/1 hypospadiasis. These data do not support an association between vaginal butoconazole use and congenital birth defects. Unfortunately, the study results have not been published, but are cited as „personal communication from F. Rosa, FDA 1993" in a reference textbook [Briggs, 2011].

Recommendations on butoconazole use in pregnancy

In the currently approved Summary of Product Characteristics in Hungary (OGYI/42622/2011, date 17 January 2011) the first trimester of pregnancy is a contraindication, with the following recommendations in pregnancy:

> 4.6 Fertility, pregnancy and lactation
>
> Pregnancy: There are limited amount of data from the use of butoconazole nitrate in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Gynazol 20mg/g vaginal cream should not be used during the first trimester of pregnancy, or in women of childbearing potential unless adequate contraception is employed. In the second and third trimester of pregnancy Gynazol 20mg/g vaginal cream should be used only if the potential benefit justifies the potential risk to the foetus.

However, the previously approved Summary of Product Characteristics of Gynazol was less restrictive on it's use in the first trimester, recommending an individual risk-benefit assessment by the treating physician (OGYI 13840/41/2005, date 02 August 2005) [OGYI, 2005]. Therefore, it is reasonably expected that a non-negligible fraction of pregnant women were exposed to butoconazole in the first trimester in the investigated time period.

Expected contribution of the current study to the filling of the gaps in current knowledge

This is the first study providing epidemiologic human data on main pregnancy outcomes in butoconazole-exposed women, complying with the requirements of the Guideline on the Exposure to Medical Products During Pregnancy: Need for Post-Authorisation Data (EMEA/CHMP/313666/2005).

The study intends to confirm the results of the F. Rosa study described in [Briggs, 2011] (i.e. to confirm the lack of teratogenic potential of locally applied butoconazole in humans).

In addition, a dedicated case-control analysis is also planned on the risk of spontaneous abortion in butoconazole-exposed pregnancies (first human data in this respect).

The study investigates multiple anti-infective gynecology products in the same setting, allowing a comparative assessment of the butoconazole results. (Previous comparative studies of gynecologic anti-infectives have not included butoconazole in their analyses).

Several high-quality nested case-control analyses have been published previously on the potential teratogenic effects of various drugs and conditions in the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA, 1980 - 1996) [Acs N, 2009a; Acs N, 2009b; Acs N, 2010; Banhidy F, 2007; Banhidy F, 2011a; Banhidy F, 2011b; Banhidy F, 2011c; Czeizel AE, 2004]. Drug exposure in these analyses was assessed based on prenatal maternal care logbooks, other medical records, and retrospective self-reported maternal information. Confounding factors of maternal age, employment status, birth order, fever-related influenza or common cold and acute maternal disease, in addition to some drug treatment (e.g. folic acid) were also carefully considered.

In the present study, HCCSCA 1980 – 1996 records are unfortunately not relevant due to the late appearance of butoconazole on the Hungarian market (2004). In the relevant years (2005 – 2013) the available datasets of the case-control surveillance of congenital anomalies (HCCSCA database) do not contain any case with recorded butoconazole exposure (official statement from NIHD based on current HCAR / HCCSCA data search [National Institute for Health Development, 2013]). Therefore, the current study is based on the National Health Insurance Fund Administration Database (OEP database). This is the first study with the intention to determine pregnancy outcomes, pregnancy periods, drug exposure, and confounding factors solely from the OEP database. The proposed, OEP-based approach may be useful also for the investigation of other drugs authorised after 1996.

8. Research question and objectives

The study has two co-primary objectives:

- to evaluate butoconazole treatment as a potential teratogenic risk factor in a population-based case-control study in Hungary, based on the OEP database;
- to evaluate butoconazole treatment as a potential risk factor of spontaneous abortion in a population-based case-control study in Hungary, based on the OEP database.

Crude and adjusted odds ratios will be calculated for both of these co-primary objectives, with several sensitivity analyses and several alternative definitions of relevant drug exposure periods. Results of all these analyses will be evaluated together, to allow for robust conclusions. Any positive finding in these analyses will be interpreted in the context of similar findings with therapeutic comparators. Nevertheless, two formal hypotheses are tested as co-primary endpoints of the study:

Formal hypothesis on teratogenic risk:

- 95% CI of the adjusted* odds ratio of foetal defect/congenital abnormality in pregnancies exposed to butoconazole in the first trimester (vs. not exposed pregnancies) will include the value 1.00 in the main analysis of teratogenicity risk (Section 9.7.10.).

  **Odds ratio adjusted for: maternal age, miconazole / clotrimazole / nystatin / local metronidazole / systemic metronidazole exposure in the first trimester; and a propensity score of the following: evidence of previous live birth, spontaneous abortion, and/or maternal diabetes in the last 4 years, evidence of acute infection / inflammatory disease in the first trimester, calendar effect (year and month).*

Formal hypothesis on spontaneous abortion risk:

- 95% CI of the adjusted** odds ratio of spontaneous abortion in pregnancies exposed to butoconazole (vs. not exposed pregnancies) will include the value 1.00 in the main analysis of spontaneous abortion risk (Section 9.7.2).

  ***Odds ratio adjusted for: maternal age, miconazole / clotrimazole / nystatin / local metronidazole / systemic metronidazole and/or diclofenac / naproxen / any NSAID exposure in the same time period; and a propensity score of the following: evidence of previous live birth, spontaneous abortion, elective termination, infertility treatment, and/or maternal diabetes in the last 4 years, evidence of more than one foetus in the current pregnancy; calendar effect (year and month).*

Secondary objectives of the study include:

- to evaluate other gynecology anti-infectives (clotrimazole, miconazole, nystatin, metronidazole) as risk factors of teratogenicity for comparative assessment, in the same setting;
- to evaluate other gynecology anti-infectives (clotrimazole, miconazole, nystatin, metronidazole) as risk factors of spontaneous abortion for comparative assessment, in the same setting;
- to collect epidemiologic data on main outcomes of butoconazole exposed pregnancies (in compliance with the Guideline on the Exposure to Medical Products During Pregnancy: Need for Post-Authorisation Data (EMEA/CHMP/313666/2005).

Study results are intended to be generalised to the European population.

9. Research methods

9.1. Study design

This study collects human epidemiologic data on main outcomes of butoconazole exposed pregnancies, in compliance with the Guideline on the Exposure to Medical Products During Pregnancy: Need for Post-Authorisation Data [EMEA/CHMP, 2005].

A retrospective analysis is planned, to avoid the time-consuming process of building a pregnancy registry prospectively.

The study includes two case-control analyses with a range of pre-defined confounder factors and sensitivity analyses. For a brief overview, please see the Table below. For more details, please see the indicated Sections of the protocol.

cases	**controls**	**database**	**drug exposure**	**Protocol section**
spontaneous abortions	live births *(live births + stillbirths)*	OEP, 2005-2011.	120 days before index date *(60 or 30 days before index date)* [Index date in cases: date of spontaneous abortion. Index date in controls: 180 days before live birth.]	9.7.2.
foetal defects and congenital anomalies	live births without congenital anomaly *(live births and stillbirths without congenital anomaly)*	OEP, 2005-2011.	1st month, 2nd month, 3rd month, 2nd+3rd month, first trimester, after first trimester *(Day 1 of pregnancy: +2 weeks or -2 weeks)*	9.7.10.

(Italics: sensitivity analyses)

Rationale to select the case-control design (instead of a retrospective cohort study):
The case-control study design represent an accepted and recommended approach for the investigation of drug effects on pregnancy outcomes in the postmarketing phase [EMEA/CHMP, 2005]. To study a drug effect on pregnancy outcomes in the OEP database, first the pregnancy outcome and it's date must be determined. This information, together with the reported date of obligatory gynecology investigation (AFP screening test) in the case of late pregnancy outcomes can be used to categorize previous drug exposures according to the relevant time periods of pregnancy (i.e. first/second/third trimester).

The current study is a MAH-initiated, retrospective post-authorization safety study (PASS), based on the analysis of an existing database. In Hungary, the authorized body for the

professional and ethical approval of MAH-initiated, national PASS studies is the National Institute for Quality- and Organizational Development in Healthcare and Medicines - National Institute of Pharmacy (GYEMSZI-OGYI). The study protocol will be registered in the EU PAS register before the start of data collection, and the study results will also be submitted once the final study report has been finalised.

9.2. Setting

Persons and place:
All pregnancies and births in Hungary reported to the National Healthcare Fund (OEP) in the investigated time period (see below).

Time period:
All pregnancy outcomes reported to the National Healthcare Fund (OEP) between 01 January 2005 and 31 December 2011 (inclusive). Rationale: Butoconazole became available in Hungary in 2004, and a 1-year follow-up is planned after all pregnancy outcomes (to collect the diagnoses and late reports of congenital anomalies until the age of 1 year). In addition, selected confounding factors will also be evaluated in the last 4 years before all pregnancy outcomes, i.e. from 01 January 2001 the earliest. Rationale: OEP data quality and structure significantly changed over time, not supporting the use of OEP records for the intended purpose in years before 2001.

Selection criteria:
All pregnancy outcome categories (as defined by the Guideline on the Exposure to Medical Products During Pregnancy: Need for Post-Authorisation Data [EMEA/CHMP, 2005]) are included in the study.

Exclusion criteria:
Cases exposed to other drugs / other risk factors are not excluded from the study. Instead, a range of confounding factors is included in the statistical analyses (see Section 9.7).

9.3. Variables

Pregnancy outcomes

According to the relevant guideline [EMEA/CHMP, 2005], pregnancy outcomes to be evaluated in the postmarketing phase include the following eight categories:

- ectopic pregnancy
- spontaneous abortion
- elective termination (foetal defects)
- elective termination (no foetal defects or unknown)
- stillbirth with foetal defects
- stillbirth without foetal defects
- live birth with congenital anomaly
- live birth without congenital anomaly

For the technical definitions of these outcomes in the OEP database, please see Annex 3.1. It is expected that the provided definitions cover the vast majority of pregnancies in the relevant time period (an exception is mola hydatiosa which is not investigated in this study, in line with the CHMP guideline [EMEA/CHMP, 2005].

All relevant HCAR / HCCSCA database records will also be assigned to one of these outcomes by the HCAR / HCCSCA personnel, based on the medical content of the records.

Birth weight data in the OEP database will also be analysed. For more details, please see Section 9.7.11.

Time periods of the pregnancy

According to the relevant guideline [EMEA/CHMP, 2005], all studies should try to address drug exposure in specified time periods of the pregnancy:

- Before conception
- First trimester
- After first trimester
- During all pregnancy
- Unknown

Depending on the pregnancy outcome, different time periods are of particular concern. The analysis of spontaneous abortion in the current study follows the design of a published large-scale study (Rosa 1987), with a drug exposure period of 120 days before index date (where index date is the date of spontaneous abortion in cases, and a corresponding date with a similar gestational age in controls – for details, please see Section 9.7.2.). For the analysis of teratogenic effects, separate analyses for the 1st month, 2nd month, 3rd month, 2nd + 3rd month are also included. For more details and justifications, please see Section 9.7. and Annex 3.2.

Investigated drugs

- butoconazole (test drug)
- clotrimazole, miconazole, nystatin, metronidazole (therapeutic controls)
- other drugs e.g. diclofenac, naproxen, any NSAID (confounding factors)

Note that the current analysis of the OEP database is technically limited to medicinal products with available patient-level records (i.e. non-prescription drugs are not analysed). For the discussion of this limitation, please see Section 9.9.

One of the therapeutic control drugs (metronidazole) is available both in locally administered and systemic formulations (e.g. as oral tablet or as i.v. infusion). In this study, local and systemic metronidazole formulations will be analysed separately.

Drug exposure is analysed as a binary parameter (yes/no) based on the evidence of at least one prescription refill in the OEP database in the relevant time periods.

Investigated confounding factors

According to a recent review on the problem of confounding in studies of the effect of maternal drug use on pregnancy outcome [Kallen B, 2012], several confounding factors shall also be considered when the effect of maternal drug use on pregnancy outcome is investigated. Confounding factors are partly different for all pregnancy outcomes (e.g. spontaneous abortion, teratogenic effect, ectopic pregnancy). To lower the number of independent variables in the statistical models, most confounding factors will not be analysed separately but will be integrated into appropriate propensity scores. For more details, please see Section 9.7.

9.4. Data sources

Several high-quality nested case-control analyses have been published previously on the potential teratogenic effects of various drugs and conditions in the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA, 1980 - 1996) [Acs N, 2009a; Acs N, 2009b; Acs N, 2010; Banhidy F, 2007; Banhidy F, 2011a; Banhidy F, 2011b; Banhidy F, 2011c; Czeizel AE, 2004]. Drug exposure in these analyses was assessed based on prenatal maternal care logbooks, other medical records, and retrospective self-reported maternal information. Confounding factors of maternal age, employment status, birth order, fever-related influenza or common cold and acute maternal disease, in addition to some drug treatment (e.g. folic acid) were also carefully considered.

In the present study, HCCSCA 1980 – 1996 records are unfortunately not relevant due to the late appearance of butoconazole on the Hungarian market (2004). In the relevant years (2005 – 2013) the available datasets of the case-control surveillance of congenital anomalies (HCCSCA database) do not contain any case with recorded butoconazole exposure (official statement from NIHD based on current HCAR / HCCSCA data search [National Institute for Health Development, 2013]).

Therefore, the current study is based on the National Health Insurance Fund Administration Database (OEP database). The OEP database contains individual data on the insured Hungarian population regarding their (obligatory) national health insurance funded medical service use, including outpatient prescription medicine claims (note that inpatient prescription medicine claims are hardly reported to OEP), and all inpatient and outpatients visits and investigations (except for general practitioner visits). The medical validity of a payer's database may be compromised by financial aspects whenever the reports are compiled by service providers. Nevertheless, the investigated eight pregnancy outcomes are hard endpoints which are clearly distinguishable and are reliably reported in the clinical practice, according to the expert opinion of the Principal Investigator (Nándor Ács MD PhD med habil). Regarding the validity of reports on diabetes (a confounding factor in the analyses), the reports of service use in a sufficiently long period are also considered to be a valid indicator of the disease (for technical definitions, please see Annex 3.3.2. and Annex 3.4.2.). Maternal age, another important confounding factor is considered to be reliable in the OEP database. Prescription claims in the database are also considered sufficiently valid, given that the prescriptions clearly identify the type of drug prescribed, and that patient co-payment level is significant. The question is of course the gap between a claimed prescription and a medicine taken. Another limitation is the lack of information on non-prescription drug use.

It is important to mention that the OEP database does not contain data on the date of the last menstrual period before the pregnancy outcome, therefore the gestational age in this database is determined indirectly, based on the reported date of obligatory gynecology investigations (for details, please see Annex 3.2.).

9.5. Study size

According to national statistics provided by Hungarian Central Statistical Office, the following numbers of pregnancy outcomes occurred in the relevant time period:

	2005	2006	2007	2008	2009	2010	2011	Total
Live birth	97 496	99 871	97 613	99 149	96 442	90 335	88 049	668 955
Foetal death*	17 528	17 847	17 247	17 714	17 885	16 710	17 220	122 151
Termination of pregnancy	48 689	46 324	43 870	44 089	43 181	40 449	38 443	305 045
Total pregnancy outcomes	163 713	164 042	158 730	160 952	157 508	147 494	143 712	1 096 151

**Foetal death in the Hungarian Central Statistical Office statistics include: ectopic pregnancy, spontaneous abortion, stillbirth.*

Altogether almost 1 100 000 pregnancy outcomes occurred in the evaluated time period (of these, 668 955 live births). The total number of foetal deaths was around 122 000 (including ectopic pregnancy, spontaneous abortion, and stillbirth cases). It is expected that most of these cases are included in the OEP database. Accordingly, the size of the current study is similar to a recently published population-based analysis in Denmark (1 221 546 pregnancy outcomes, [Nybo Andersen AM, 2000]) and is about one order of magnitude larger than the largest published study on other gynecology anti-infectives (104 339 pregnancies, [Rosa FW, 1987]. The single published human study on butoconazole investigated 229 101 completed pregnancies and found no increased risk in women with first-trimester butoconazole exposure [Briggs, 2011].

No formal sample size calculation was performed for the current study. To maximize the power and to avoid selection bias, all pregnancies in the relevant time period are included. The expected size of the study is considered to be adequate, i.e. similar or larger than previous published studies on adverse drug effects in pregnancy.

9.6. Data management

The screening and processing of individual–level data in the OEP database will be performed directly by OEP personnel, running of PL/SQL scripts provided by RxTarget Kft. The scripts will analyse inpatient, outpatient and prescription drug usage records, linked to each other via individual TAJ numbers of the patients. All statistical and analytical processing of the data will be done on OEP servers, including all intermediate tables and listings.

In agreement with the data protection standards of the OEP, no individual-level data but only aggregated group statistics and statistical model results will be available to non-OEP personnel. Descriptive statistics will not be provided on groups smaller than 10 patients.

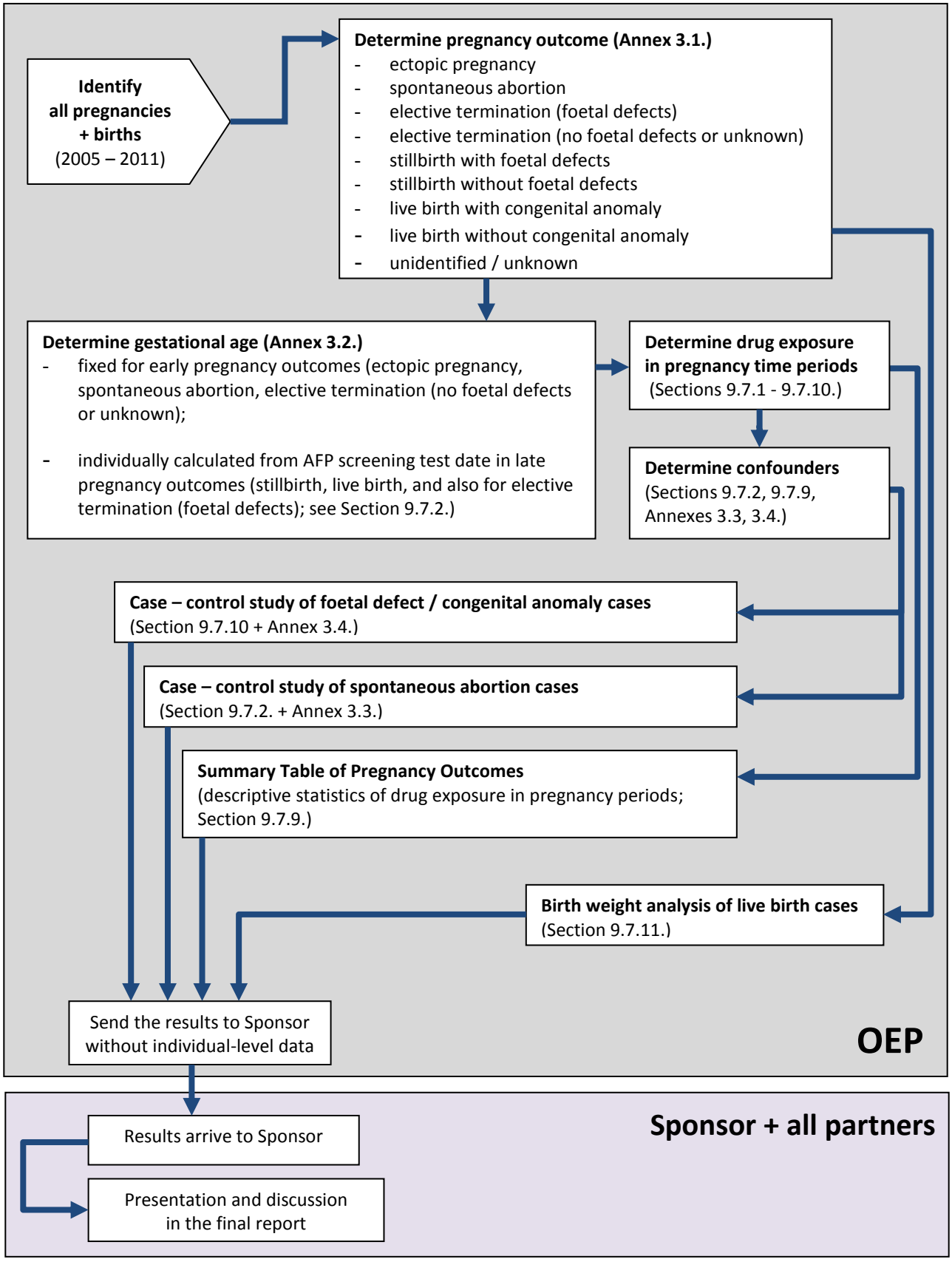
Inductive statistical results will be generated using the following statistical software, installed on OEP computers:

- R Core Team (2012). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org/.

9.7. Data analysis

The planned analyses comprise descriptive statistics of drug exposure in pregnancies with different pregnancy outcomes, analysis of birth weight in unexposed and drug-exposed pregnancies, and case-control studies on spontaneous abortion and congenital abnormalities considering a range of confounding factors and sensitivity analyses. A schematic flowchart of these analyses is presented below, while a detailed description is provided in Sections 9.7.1. – 9.7.11 and in Annexes 3.1. – 3.4.

Schematic flowchart of the planned analyses



9.7.1. Ectopic pregnancies

Ectopic pregnancies will be identified based on the technical definitions of pregnancy outcomes as provided in Annex 3.1.

To investigate a potential drug effect on the relative rate of ectopic pregnancies, drug exposure around the time of implantation is of particular concern. Implantation typically occurs on days 21 to 26 of pregnancy, i.e. until the 12th day after ovulation [Papp Z, 1999].

Ectopic pregnancy is typically diagnosed after 7 (SD 2) weeks of amenorrhoea [Tay JI, 2000] which refers to weeks 6-10 of pregnancy. The gestational age of ectopic pregnancies is hardly documented in payers' databases and registries. In a previous retrospective analysis in Denmark comprising 1 221 546 pregnancy outcomes, the gestational age of recognised ectopic pregnancies was set as 8 weeks at diagnosis in all cases [Nybo Andersen AM, 2000].

Ectopic pregnancies with a refilled prescription of the investigated drug in the potentially relevant time period, i.e. in the last 8 weeks before the reported outcome will be considered to be „drug exposed". The timing of drug exposure in drug-exposed cases will be classified as a „unknown" due to the inevitable mix of „before conception" and early „first trimester" exposures in this analysis.

The results of the analysis of ectopic pregnancies will be presented in the Summary Table of Pregnancy Outcomes as shown in Section 9.7.9, separately for all tested drugs. These results will be interpreted in the context of alternative pregnancy outcomes (i.e. relative frequency of ectopic pregnancy).

There are several known risk factors of ectopic pregnancy, including previous ectopic pregnancy, history of pelvic inflammatory disease, tubal damage from infection or surgery, a history of infertility, treatment for in vitro fertilisation, increased age, smoking. Previous female sterilisation and current use of an intrauterine contraceptive device are also risk factors when patients with ectopic pregnancy are compared with pregnant controls [Tay JI, 2000]. However, no further statistical analysis is planned on this pregnancy outcome beyond the collection of frequency data on drug-exposed and unexposed ectopic pregnancies, because the available non-clinical and clinical data do not raise concerns about any association between butoconazole use and ectopic pregnancy.

9.7.2. Spontaneous abortions

The analysis of spontaneous abortions follows the methods described by Rosa et al [Rosa FW, 1987] for clotrimazole, miconazole, nystatin and other gynecology anti-infectives, i.e. comparisons to normal delivery cases, with the following modifications:

Main analysis of spontaneous abortions	
definition of cases	All spontaneous abortions in the OEP database in the tested time period (2005-2012). For the technical definition of spontaneous abortion, please see Annex 3.1.
definition of controls	Live births with at least 180-day history of the mother in the OEP database before delivery in the relevant time period. For the technical definition of live births (including live births with / without congenital anomaly), please see Annex 3.1.
index date	in cases: reported date of spontaneous abortion. in controls: reported date of live birth minus 180 days.
drug exposure criteria	Prescription claim (Rx) in the first trimester defined as a 120-day period before index date.

In addition, the following sensitivity analyses are planned, to test the robustness of the results:

Sensitivity analyses of spontaneous abortions	
analysis ID	**Alterations from the main analysis**
Spontab_sensitivity_1	drug exposure period narrowed to 60 days before index date
Spontab_sensitivity_2	drug exposure period narrowed to 30 days before index date
Spontab_sensitivity_3	controls include all live births and stillbirths
Spontab_sensitivity_4	index date for controls: reported date of delivery minus 200 days; in addition, cases and controls must have at least one OEP-reimbursed service 70-250 days before index date. (Replication of the published sensitivity analysis of the Rosa study).
Spontab_sensitivity_5	cases and controls restricted to pregnancies with reported AFP screening test. Drug exposure criteria: prescription claim (Rx) in the last 16 weeks before reported date of AFP screening test.
Spontab_sensitivity_6	cases also include pregnancies without identified pregnancy outcome (see Section 9.7.9.). In cases without identified pregnancy outcome, index date is defined as the date of the last pregnancy-related condition/intervention* plus 30 days.

**Pregnancy-related conditions/interventions are listed in Annex 3.2. at the criteria of „late AFP reporting" pregnancies.*

The main analysis and the sensitivity analyses will include the following test variables:

- Exposure to gynecology anti-infectives within the drug exposure period
  - butoconazole (yes/no)
  - miconazole (yes/no)
  - clotrimazole (yes/no)
  - metronidazole (local) (yes/no)
  - metronidazole (systemic) (yes/no)
  - nystatin (yes/no)

- Exposure to non-aspirin NSAIDs within the drug exposure period
  - diclofenac (yes/no)
  - naproxen (yes/no)
  - any NSAID (yes/no)

- Maternal age at index date (in 5-year intervals, as a nominal parameter).

The analyses will also take efforts to consider other confounding variables, integrated into an appropriate „propensity score". For details, please see Annex 3.3. Note that some potential confounding factors (including age at menarche, gestational age, maternal education, maternal marital status, alcohol use, smoking, caffeine use, illicit drug use, body mass index, social class) will not be included in the models because of the lack of adequate data in the OEP database. Note that it is not expected that these factors are associated with both the pregnancy outcome and drug exposure [Clark CA, 2011b]. For justifications of the planned analysis, please see Annex 3.3.1.

The indication treated may also be a confounding factor. It is medically plausible that vaginal fungal infections represent an independent risk factor for spontaneous abortion themselves, and/or may occur more frequently in women carrying other risk factors for spontaneous abortion (e.g. malnutrition, systemic antibiotic drug treatment, or promiscuity). The included therapeutic controls clotrimazole, miconazole, or nystatin are especially important in this respect: any elevation of the risk of spontaneous abortions in butoconazole exposed pregnancies will be interpreted in the context of the same risk in pregnancies exposed to therapeutic controls. Note that in a previous clinical study, increased risk of spontaneous abortion was reported for clotrimazole (OR 1.34, 95% CI 1.1 – 1.7) and miconazole (OR 1.36, 95% CI 1.1 – 1.6), and this apparently elevated risk could be drug-related or indication related.

To adjust for the confounder(s) in the statistical analysis, a logistic regression model will be applied, as recommended in a recent review on the problem of confounding in studies of the effect of maternal drug use on pregnancy outcome [Kallen B, 2012]. The logistic regression model is a regression method to predict outcome (e.g. rate of congenital malformations) as influenced by one or more confounding factors. Logistic regression is used in analyses aiming at risk determinations in a dichotomous situation, for example, presence or absence of a malformation [Kallen B, 2012].

For all analyses, odds ratios with 95% confidence intervals will be calculated (both as crude and adjusted values) as shown below.

Variable	Controls N=	Cases N=	OR (95% CI)		
			crude	adjusted (1)	adjusted (2)
Type of gynecology anti-infectives					
none	N (%)	N (%)	1.00	1.00	1.00
butoconazole	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
clotrimazole	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole (local)	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole (systemic)	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Type of non-aspirin NSAIDs					
none	N (%)	N (%)	1.00	1.00	1.00
diclofenac	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
naproxen	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
any NSAID	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Maternal age at index date					
15-19	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
20-24	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
25-29	N (%)	N (%)	1.00	1.00	1.00
30-34	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
35-39	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
40-45	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)

(1) adjusted for test factors and confounders which are presented in the table;
(2) in addition, also adjusted for all other investigated confounder factors (the latter have been integrated into a single propensity score before adjustment).

Separate tables will be presented for the main analysis and for all sensitivity analyses.

In addition, the number of spontaneous abortions from the main analysis will be included in the Summary Table of Pregnancy Outcome, separately for all tested drugs. The timing of drug exposure in drug-exposed cases will be classified as „unknown", due to the inevitable mix of first trimester, second trimester and „before conception" exposures in this analysis (for more details on the Summary Table, please see Section 9.7.9).

9.7.3. Elective termination (no foetal defects or unknown)

Cases with elective termination (no foetal defects or unknown) will be identified in the OEP database according to the technical definitions described in Annex 3.1.

Similarly to the Rosa study [Rosa FW, 1987], those elective terminations with a refilled prescription of the investigated drug in the last 120 days before the reported outcome will be considered to be „drug exposed". The timing of drug exposure in drug-exposed cases will be classified as „unknown" due to the inevitable mix of first trimester, second trimester and „before conception" exposures in this analysis.

The number of elective terminations (no foetal defects or unknown) will be included in the Summary Table of Pregnancy Outcomes, separately for all tested drugs. For more details, please see Section 9.7.9.

Beyond the collection of frequency data on drug-exposed and unexposed elective terminations, no further statistical analysis is planned on this pregnancy outcome.

9.7.4. Elective termination (foetal defects)

Cases with „elective termination (foetal defects)" will be identified in the OEP database according to the technical definitions described in Annex 3.1.

In cases with a reported AFP test in the last 26 weeks before elective termination due to foetal defects, the first day of pregnancy will be determined as follows:

analysis ID	**First day of pregnancy**
main analysis	{AFP reported date} minus 121 days
CA_sensitivity_1	{AFP reported date} minus 135 days
CA_sensitivity_2	{AFP reported date} minus 107 days

In pregnancies with late AFP reports alternative Day 1 estimates may be allowed in line with Annex 3.2.

In cases without a reported AFP test in the last 26 weeks before outcome, the gestational age at elective termination due to foetal defects will be assumed to be 14 weeks in the main analysis, and also in sensitivity analyses 1-3 and 5. For justifications, please see Annex 3.2. In an additional sensitivity analysis (CA_sensitivity_4), cases and controls without a reported AFP test in the last 26 weeks of pregnancy will be excluded from the analysis.

The number of elective terminations due to foetal defects in the main analysis will be included in the Summary Table of Pregnancy Outcomes, separately for all tested drugs. Drug exposure periods will be analysed based on the calculated first day of pregnancy. For more details, please see Section 9.7.9.

Elective terminations due to foetal defects (together with stillbirths with foetal defects, and with live births with congenital anomalies) will also be included in a multivariate analysis of the risk of drug induced congenital anomalies. The details of this analysis is described in Section 9.7.10.

9.7.5. Stillbirth with foetal defects

Cases of stillbirth with foetal defects will be identified in the OEP database according to the technical definitions described in Annex 3.1.

In cases with a reported AFP test in the last 26 weeks before stillbirth, the first day of pregnancy will be determined as follows:

analysis ID	**First day of pregnancy**
main analysis	{AFP reported date} minus 121 days
CA_sensitivity_1	{AFP reported date} minus 135 days
CA_sensitivity_2	{AFP reported date} minus 107 days

In pregnancies with late AFP reports alternative Day 1 estimates may be allowed, as specified in Annex 3.2.

Cases without a reported AFP test in the last 26 weeks before stillbirth will be assumed to have the average gestational age of "stillbirth with foetal defects" cases with reported AFP screening test in the relevant period in the main analysis and in sensitivity analyses, except for CA_sensitivity_4 where cases and controls without a reported AFP test in the last 26 weeks of pregnancy will be excluded from the analysis. For justifications, please see Annex 3.2.

The number of stillbirths with foetal defects in the main analysis will be included in the Summary Table of Pregnancy Outcomes, separately for all tested drugs. Drug exposure periods will be analysed based on the calculated first day of pregnancy. For more details, please see Section 9.7.9.

Stillbirths with foetal defects (together with elective terminations due to foetal defects, and with live births with congenital anomalies) will also be included in a multivariate analysis of the risk of drug induced congenital anomalies. The details of this analysis is described in Section 9.7.10.

9.7.6. Stillbirth without foetal defects

Cases of stillbirth without foetal defects will be identified in the OEP database according to the technical definitions described in Annex 3.1.

In cases with a reported AFP test in the last 26 weeks before stillbirth, the first day of pregnancy will be determined as follows:

analysis ID	**First day of pregnancy**
main analysis	{AFP reported date} minus 121 days
CA_sensitivity_1	{AFP reported date} minus 135 days
CA_sensitivity_2	{AFP reported date} minus 107 days

In pregnancies with late AFP reports alternative Day 1 estimates may be allowed, as specified in Annex 3.2.

Cases without a reported AFP test in the last 26 weeks before stillbirth will be assumed to have the average gestational age of "stillbirth without foetal defects" cases with reported AFP screening test in the relevant period in the main analysis and in sensitivity analyses, except for CA_sensitivity_4 where cases and controls without a reported AFP test in the last 26 weeks of pregnancy will be excluded from the analysis. For justifications, please see Annex 3.2.

The number of stillbirths without foetal defects in the main analysis will be included in the Summary Table of Pregnancy Outcomes, separately for all tested drugs. Drug exposure periods will be analysed based on the calculated first day of pregnancy. For more details, please see Section 9.7.9.

Stillbirths without foetal defects (together with live births without congenital anomalies) will also be included in a multivariate analysis of the risk of drug induced congenital anomalies, as part of the control group in a sensitivity analysis. The details of this analysis is described in Section 9.7.10.

9.7.7. Live birth with congenital anomaly

Cases of live birth with congenital anomaly will be identified in the OEP database according to the technical definitions described in Annex 3.1.

In cases with a reported AFP test in the last 26 weeks before the outcome, the first day of pregnancy will be determined as follows:

analysis ID	**First day of pregnancy**
main analysis	{AFP reported date} minus 121 days
CA_sensitivity_1	{AFP reported date} minus 135 days
CA_sensitivity_2	{AFP reported date} minus 107 days

In pregnancies with late AFP reports alternative Day 1 estimates may be allowed, as specified in Section 9.7.2. and Annex 3.2.

Cases without a reported AFP test in the last 26 weeks before live birth will be assumed to have the average gestational age of "live birth with congenital anomaly" cases with reported AFP screening test in the relevant period in the main analysis and in sensitivity analyses, except for CA_sensitivity_4 where cases and controls without a reported AFP test in the last 26 weeks of pregnancy will be excluded from the analysis. For justifications, please see Annex 3.2.

The number of live births with congenital anomaly in the main analysis will be included in the Summary Table of Pregnancy Outcomes, separately for all tested drugs. Drug exposure periods will be analysed based on the calculated first day of pregnancy. For more details, please see Section 9.7.9.

Live births with congenital anomaly (together with elective terminations due to foetal defects, and with stillbirths with foetal defects) will also be included in a multivariate analysis of the risk of drug induced congenital anomalies. The details of this analysis is described in Section 9.7.10.

9.7.8. Live birth without congenital anomaly

Cases of live birth without congenital anomaly will be identified in the OEP database according to the technical definitions described in Annex 3.1.

In cases with a reported AFP test in the last 26 weeks before the outcome, the first day of pregnancy will be determined as follows:

analysis ID	**First day of pregnancy**
main analysis	{AFP reported date} minus 121 days
sensitivity_1	{AFP reported date} minus 135 days
sensitivity_2	{AFP reported date} minus 107 days

In pregnancies with late AFP reports alternative Day 1 estimates may be allowed, as specified in Annex 3.2.

Cases without a reported AFP test in the last 26 weeks before live birth will be assumed to have the average gestational age of "live birth without congenital anomaly" cases with reported AFP screening test in the relevant period in the main analysis and in sensitivity analyses, except for CA_sensitivity_4 where cases and controls without a reported AFP test in the last 26 weeks of pregnancy will be excluded from the analysis. For justifications, please see Annex 3.2.

The number of live births without congenital anomaly in the main analysis will be included in the Summary Table of Pregnancy Outcomes, separately for all tested drugs. Drug exposure periods will be analysed based on the calculated first day of pregnancy. For more details, please see Section 9.7.9.

Live births without congenital anomaly will be included in a multivariate analysis of the risk of drug induced congenital anomalies as the control group. The details of this analysis is described in Section 9.7.10.

9.7.9. Summary Table of Pregnancy Outcomes

The layout of the Summary Table of Pregnancy Outcomes as defined by the Guideline on the Exposure to Medical Products During Pregnancy: Need for Post-Authorisation Data [EMEA/CHMP, 2005] is applied in this study, with the following modification: the number of not exposed cases is also included, to illustrate the baseline distribution of outcomes in the unexposed population.

Separate tables will be provided for all of the investigated drugs / drug groups (butoconazole, clotrimazole, miconazole, nystatin, metronidazole; diclofenac, naproxen, any NSAID).

In these tables, the eight investigated pregnancy outcomes will be included according to the specifications provided in Sections 9.7.1 – 9.7.8. In brief: data from sensitivity analyses will be omitted; and drug exposure period will be specified as „unknown" for cases of ectopic pregnancy, spontaneous abortion and elective termination (no foetal defects or unknown).

Similar tables containing combined analyses of OEP and HCAR / HCCSCA datasets are not provided, because the HCAR / HCCSCA dataset does not include cases of e.g. spontaneous abortion, ectopic pregnancy or stillbirth without foetal defect.

Exposure is defined as a prescription refilled in the indicated time period. Time periods in the table refer to the following gestational periods:

Time period	**Gestational days**
Before conception	last 30 days before day 1 of pregnancy
First trimester	days 1 – 84
After first trimester	after day 84
During all pregnancy	both in days 1-84 and after day 84
Unknown	any exposure in pregnancy (i.e. the time period ranging from minus 30 days before pregnancy to the date of pregnancy outcome) which can not be clearly sorted to any of the above categories.
No exposure	no exposure in the time period ranging from minus 30 days before pregnancy to the date of pregnancy outcome

The layout of the Summary Table is shown below:

Pregnancy outcome	retrospective cases (number)					
	timing of **{drug name}** exposure in pregnancy					
	Before conception	**1st trimester**	**after 1st trimester**	**during all pregnancy**	**unknown**	**not exposed cases**
Ectopic pregnancy					{exposed No.}	{not exposed No.}
Spontaneous abortion					{exposed No.}	{not exposed No.}
Elective termination (no foetal defects or unknown)					{exposed No.}	{not exposed No.}
Elective termination (foetal defects)	{exposed No.}	{exposed No.}	{exposed No.}	{exposed No.}		{not exposed No.}
Stillbirth with foetal defects	{exposed No.}	{exposed No.}	{exposed No.}	{exposed No.}		{not exposed No.}
Stillbirth without foetal defects	{exposed No.}	{exposed No.}	{exposed No.}	{exposed No.}		{not exposed No.}
Live birth with congenital anomaly	{exposed No.}	{exposed No.}	{exposed No.}	{exposed No.}		{not exposed No.}
Live birth without congenital anomaly	{exposed No.}	{exposed No.}	{exposed No.}	{exposed No.}		{not exposed No.}
Unidentified / unknown outcome					{exposed No.}	{not exposed No.}

{exposed No.}: Number of cases belonging to the indicated time period
{not exposed No.}: Number of cases not exposed in any of the indicated time periods.

Unidentified / unknown outcome: there are several reasons which can lead to the lack of identified pregnancy outcome in the OEP database, including e.g. the use of private healthcare services in Hungary, the use of healthcare services in other country, or missed reporting of an occurred pregnancy outcome (e.g. a non-documented early spontaneous abortion). Among these, spontaneous abortion is the medically most important situation. Therefore, all cases without identified outcome will be assumed to be spontaneous abortions in a sensitivity analysis of the spontaneous abortion case-control analysis (see Section 9.7.2.).

In „unidentified / unknown outcome" cases, the timing of drug exposure will be categorized as „unknown" if there is a relevant prescription claim (Rx) in the last 90 days *before* and/or in the first 30 days *after* the date of the last report indicating an ongoing pregnancy. Without prescription claim in the indicated period, the timing of drug exposure will be categorized as „none".

Relative frequencies (%) of the eight investigated pregnancy outcomes will also be calculated and plotted vs. other drugs/drug groups:

- in the first trimester
- after first trimester
- during all pregnancy
- any time during pregnancy*

*: any time during pregnancy: sum of cases exposed before conception, in the first trimester, after the first trimester, during all pregnancy, and unknown.

9.7.10. Multivariate analysis of drug induced risk of congenital anomalies

The intention of the study is to evaluate the total (neonatal + foetal) risk of congenital anomalies in the offspring of mothers who were exposed to the tested drugs. All pregnancy outcomes in these analyses will be identified based on the technical definitions of pregnancy outcomes as provided in Annex 3.1. The following analyses are planned:

<table>
<tr><th colspan="2">Planned analyses of spontaneous abortions</th></tr>
<tr><th colspan="2">Main analysis</th></tr>
<tr><td colspan="2">Cases = Elective termination (foetal defects), Stillbirth with foetal defects, Live birth with congenital anomaly.
Controls = Live birth without congenital anomaly
Day 1 of pregnancy = {AFP reported date} minus 121 days; in pregnancies with late AFP reports an alternative Day 1 estimate will be applied (as specified in Annex 3.2.).</td></tr>
<tr><th colspan="2">Alterations from the main analysis in sensitivity analyses</th></tr>
<tr><td>CA_sensitivity_1*</td><td>Day 1 of pregnancy = {AFP reported date} minus 135 days</td></tr>
<tr><td>CA_sensitivity_2*</td><td>Day 1 of pregnancy = {AFP reported date} minus 107 days</td></tr>
<tr><td>CA_sensitivity_3*</td><td>Controls = live births without congenital anomaly, stillbirths without foetal defect</td></tr>
<tr><td>CA_sensitivity_4*</td><td>Cases and controls without reported AFP screening test in the last 26 weeks before pregnancy outcome are excluded from the analysis</td></tr>
<tr><td>CA_sensitivity_5*</td><td>Cases = Stillbirth with foetal defects, Live birth with congenital anomaly.</td></tr>
<tr><td>CA_sensitivity_6*</td><td>Cases = Elective termination (foetal defects), Stillbirth with foetal defects, Live birth with congenital anomaly, restricted to cases with at least one of the following anomalies / interventions reported in the offspring:

BNO Q35 cleft palate
BNO Q36 cleft lip
BNO Q37 cleft lip, cleft palate
OENO 52750 Lágyszájpadplasztika
OENO 52751 Keményszájpadplasztika
OENO 52752 Kemény- és lágyszájpadplasztika, egy ülésben
OENO 52753 Szájpadrekonstrukció, előzetes műtét után
OENO 58981 Oldalsó inkomplett ajakhasadék zárása
OENO 58982 Ajak és külső száj plastica, Le Mesurier szerint
OENO 58983 Ajak és külső száj plastica, Millard szerint
OENO 58984 Ferde archasadék (macrostoma) korrekciója
OENO 58985 Ajak- és külső szájplasztika
OENO 58986 Ajakkorrekció ajakplasztika után
OENO 58987 Median ajakhasadék zárása</td></tr>
<tr><td>CA_sensitivity_7*</td><td>Cases = Elective termination (foetal defects), Stillbirth with foetal defects, Live birth with congenital anomaly, restricted to cases with at least one of the following anomalies / interventions reported in the</td></tr>
</table>

	offspring: BNO Q7920 exomphalos BNO Q7930 gastroschisis BNO Q7940 prune belly syndrome BNO Q7950 other congenital anomalies of the abdominal wall OENO 55340 Hernioplastica umbilicalis OENO 55350 Reconstructio parietis abdominis OENO 55358 Gastroschisis műtéte OENO 55359 Omphalocele műtéte OENO 55360 Reconstructio parietis abdominis c. implant. OENO 55361 Reconstructio laparoscopica parietis abdominis cum implantate OENO 55369 Reconstructio laparoscopica parietis abdominis cum conversione
CA_sensitivity_8*	Cases = Live birth in 2005, with foetal defect / congenital anomaly reported until the end of 2012; Controls = Live birth in 2005, foetal defect / congenital anomaly not reported until the end of 2012.
CA_sensitivity_9	Cases and controls fulfilling the criteria of „late AFP reporting" (see in Annex 3.2.) are excluded.

** In pregnancies with late AFP reports an alternative Day 1 estimate will be applied, as specified in Annex 3.2.*

Rationale for these sensitivity analyses is provided in Annex 3.4.

Drug exposure in the following periods will be evaluated: first trimester [Nelson MM, 1971; van Gelder MM, 2011], first month (before organogenesis) [Acs N, 2009b; van Gelder MM, 2011], second month[Czeizel AE, 1999; van Gelder MM, 2011], third month[Czeizel AE, 1999; van Gelder MM, 2011], second and third month (the critical period for congenital anomalies) [Acs N, 2009b; Banhidy F, 2007; Czeizel AE, 1999; Kazy Z, 2005], and after the first trimester [Acs N, 2009b; Kazy Z, 2005].

The main analysis and the sensitivity analyses will include the following test variables:

- Exposure to gynecology anti-infectives in the relevant time periods
  - butoconazole (yes/no)
  - miconazole (yes/no)
  - clotrimazole (yes/no)
  - metronidazole (local) (yes/no)
  - metronidazole (systemic) (yes/no)
  - nystatin (yes/no)

- Maternal age at delivery (in 5-year intervals, as a nominal parameter).

The analyses will consider the following confounding variables, integrated into a single „propensity score":

- Evidence of previous live birth in the last 4 years before the current pregnancy;
- Evidence of previous spontaneous abortion in the last 4 years before the current pregnancy;
- Evidence of maternal diabetes in the last 4 years before or during pregnancy;
- Evidence of acute infection / inflammatory disease during the first trimester of pregnancy;
- Year of birth;
- Month of birth.

The technical definitions of these confounders are provided in Annex 3.4.

In addition, descriptive statistics will be provided on all counties of Hungary (divided to „village" and „town"), with absolute and relative frequencies of cases and controls in each of these areas.

To adjust for the confounder(s) in the statistical analysis, a logistic regression model will be applied, as recommended in a recent review on the problem of confounding in studies of the effect of maternal drug use on pregnancy outcome [Kallen B, 2012]. The logistic regression model is a regression method to predict outcome (e.g. rate of congenital malformations) as influenced by one or more confounding factors. Logistic regression is used in analyses aiming at risk determinations in a dichotomous situation, for example, presence or absence of a malformation [Kallen B, 2012].

For scientific rationale, justifications, and technical definitions of the planned analyses, please see Annex 3.4.

For all analyses, odds ratio (OR) with 95% confidence intervals will be calculated (both as crude and adjusted values) as shown below. Separate tables will be presented for the main analysis and for all sensitivity analyses.

Variable	Controls N=	Cases N=	OR (95% CI)		
			crude	adjusted (1)	adjusted (2)
Type of gynecology anti-infectives					
none	N (%)	N (%)	1.00	1.00	1.00
Butoconazole					
butoconazole in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
butoconazole in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
butoconazole in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
butoconazole in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
butoconazole in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
butoconazole after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Miconazole					
miconazole in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Clotrimazole					
clotrimazole in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
clotrimazole in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
clotrimazole in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
clotrimazole in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
clotrimazole in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
clotrimazole after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Nystatin					
nystatin in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Metronidazole (local administration)					
metronidazole in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Metronidazole (systemic administration)					
metronidazole in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Maternal age at index date					
15-19 years	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
20-24 years	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
25-29 years	N (%)	N (%)	1.00	1.00	1.00
30-34 years	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)

35-39 years	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
40-45 years	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)

(1) adjusted for other drug exposure (as listed in the table) in the same pregnancy period, and for maternal age
(2) in addition, also adjusted for all other investigated confounder factors (the latter have been integrated into a single propensity score before adjustment).

In addition, the time profile of reporting congenital anomalies after birth will also be investigated. All live births reported in the first year of the study (2005) will be followed-up throughout the investigational time period (up to the end of 2012). Late reports of foetal defects / congenital anomalies (see the BNO / OENO codes as specified in Annex 3.1.) will be analysed and summarized as shown below.

Time periods	**No. of children with report in this time period or before**	**No. of children with first report in this time period**	**Relevant BNO / OENO codes in children with first report in this time period (list of codes)**
	total number of live births in 2015: {N}		
During pregnancy or at pregnancy outcome	{N}	{N}	n.a.
1-365 days after pregnancy outcome	{N}	{N}	n.a.
In the 2nd year after pregnancy outcome	{N}	{N}	{BNO1 BNO2... OENO1 OENO2...}
In the 3rd year after pregnancy outcome	{N}	{N}	{BNO1 BNO2... OENO1 OENO2...}
In the 4th year after pregnancy outcome	{N}	{N}	{BNO1 BNO2... OENO1 OENO2...}
In the 5th year after pregnancy outcome	{N}	{N}	{BNO1 BNO2... OENO1 OENO2...}
In the 6th year after pregnancy outcome	{N}	{N}	{BNO1 BNO2... OENO1 OENO2...}
In the 7th year after pregnancy outcome	{N}	{N}	{BNO1 BNO2... OENO1 OENO2...}

It is expected that the vast majority of congenital anomalies are reported during pregnancy or in the first year after birth. Nevertheless, a sensitivity analysis (CA_sensitivity_8) is planned to include the late diagnoses / late reports of congenital anomalies (See at Section 9.7.10.).

9.7.11. Analysis of birth weight

There are separate HBCS codes for birth weight categories as follows:

HBCS	Description
15 7110	Újszülött, születési súly 999 g alatt
15 7120	Újszülött, születési súly 1000-1499 g, jelentős műtéttel
15 7130	Újszülött, születési súly 1000-1499 g, jelentős műtét nélkül
15 7140	Újszülött, születési súly 1500-1999 g, jelentős műtéttel
15 715Z	Újszülött, születési súly 1500-1999 g, jelentős műtét nélkül, súlyos problémával
15 7160	Újszülött, születési súly 1500-1999 g, jelentős műtét nélkül, közepes problémával
15 7170	Újszülött, születési súly 1500-1999 g, jelentős. műtét nélkül, egyéb problémával.
15 7180	Újszülött, születési súly 2000-2499 g, jelentős műtéttel
15 719Z	Újszülött, születési súly 2000-2499 g, jelentős műtét nélkül, súlyos problémával
15 7200	Újszülött, születési súly 2000-2499 g, jelentős műtét nélkül, közepes problémával
15 7210	Újszülött, születési súly 2000-2499 g, jelentős műtét nélkül, normális újszülött diagnózissal
15 7220	Újszülött, születési súly 2000-2499 g, jelentős műtét nélkül, egyéb problémával
15 7230	Újszülött, születési súly 2499 g felett, jelentős műtéttel
15 7240	Újszülött, születési súly 2499 g felett, kisebb hasi műtéttel
15 7260	Újszülött, születési súly 2499 g felett, jelentős műtét nélkül, közepes problémával
15 7270	Újszülött, születési súly 2499 g felett, jelentős műtét nélkül, normális újszülött diagnózissal
15 7280	Újszülött, születési súly 2499 g felett, jelentős műtét nélkül, egyéb problémával
15 734Z	Újszülött, születési súly 2499 g felett, jelentős műtét nélkül, súlyos problémával, 5 napot nem meghaladó gépi lélegeztetéssel
15 735Z	Újszülött, születési súly 2499 g felett, jelentős műtét nélkül, súlyos problémával, 5 napnál hosszabb gépi lélegeztetéssel

Note that clotrimazole was shown to have a preventive effect against preterm birth and low birth weight (below 2500g) when administered in the first trimester [Czeizel AE, 2007]. Accordingly, this study investigates all gynecology anti-infectives in this respect. The absolute and relative proportions of low birth-weight cases in drug-exposed and unexposed pregnancies will be presented in contingency tables, with pre-planned statistical comparisons (Chi-square test or Fisher's exact test).

Drug = butoconazole		**Low birth weight (<2500g)**		
		Yes*	No**	Total
Drug exposure in the first trimester	Yes	N (%)	N (%)	N (%)
	No	N (%)	N (%)	N (%)
	Total	N (%)	N (%)	N (%)

*HBCS codes 15 7110, 15 7120, 15 7130, 15 7140, 15 715Z, 15 7160, 15 7171, 15 7180, 15 719Z, 15 7200, 15 7210, 15 7220;
**HBCS codes 15 7230, 15 7240, 15 7260, 15 7270, 15 7280, 15 734Z, 15 735Z

Similar tables will be provided for clotrimazole, miconazole, metronidazole (local), metronidazole (systemic), and nystatin.

In addition, more detailed descriptive statistics will be provided for all gynecology anti-infectives as shown below:

		Birth weight					
		<1000g	**1000 – 1499g**	**1500 – 1999g**	**2000-2499g**	**>2500g**	**total**
Relevant HBCS codes →		15 7110	15 7120, 15 7130	15 7140, 15 715Z, 15 7160, 15 7170	15 7180, 15 719Z, 15 7200, 15 7210, 15 7220	15 7230, 15 7240, 15 7260, 15 7270, 15 7280, 15 734Z, 15 735Z	
Drug exposure in first trimester	**none**	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	butoconazole	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	clotrimazole	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	miconazole	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	metronidazole (local)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	metronidazole (systemic)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	nystatin	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	total	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

Moreover, all available individual birth weight data reported to the OEP database will be evaluated, as shown below:

		Individual birth weight data in the OEP database			
		Not reported	**Reported**	**Mean**	**95% CI**
Drug exposure in first trimester	**none**	N (%)	N (%)	... g	... g
	butoconazole	N (%)	N (%)	... g	... g
	clotrimazole	N (%)	N (%)	... g	... g
	miconazole	N (%)	N (%)	... g	... g
	metronidazole (local)	N (%)	N (%)	... g	... g
	metronidazole (systemic)	N (%)	N (%)	... g	... g
	nystatin	N (%)	N (%)	... g	... g
	total	N (%)	N (%)	... g	... g

9.8. Quality control

The study protocol and all amendments will be submitted to the competent National Authority (GYEMSZI) for review and approval. Ethical review is included in the GYEMSZI approval process according to the Hungarian law. The study will be registered in the EU PAS register before the start of data collection. Any protocol amendments will also be submitted for GYEMSZI approval and will also be registered at EU PAS.

Quality control of data management will be ensured by the qualified personnel and the regulated workflows at the OEP and HCAR / HCCSCA. All output tables received from OEP will be included in the final report.

9.9. Limitations of the research methods

Randomised and double blinded studies in pregnant women are feasible only in exceptional cases (where the study is the best interest of both mother and infant), due to ethical considerations [EMEA/CHMP, 2005].

Case control studies identify individuals with a specific outcome (e.g. a congenital malformation), against a control group and assess both groups with respect to previous exposure. The source data of case-control studies in pregnancy can be a birth defect registry or a pregnancy registry. Different types of registries exist with respect to the timing of data collection: note that retrospective data collection is subject to *recall bias*. Some registries are set up and coordinated centrally by government agencies with obligatory reporting, while other registries (e.g. some industry or academia initiated registries) are based on voluntary reporting. Note that voluntary reporting is subject to *selection bias*.

The data source of the current study is the OEP database. Key features and limitations of this database are summarized below, together with the planned steps to balance the identified limitations.

OEP database	
Key features	**Limitations**
Coverage: The full insured population in Hungary. Covers all national health insurance funded medical service use, including prescription medicine claims, inpatient and outpatients visits and investigations (except for general practitioner visits).	lack of insurance; private healthcare services.
Pregnancy outcomes: The investigated eight pregnancy outcome categories are hard endpoints which are reliably reported to the payer's database. Recall bias is low due to the lack of retrospective	

data collection.	
First day of pregnancy: Not included in the database. May be estimated from the reported date of AFP screening test (obligatory screening test in pregnancy after the completion of week 16)	uncertainty of the calculated Day1 of pregnancy.
Exposure data: All prescription refills are recorded in the database prospectively, i.e. there is no retrospective data collection on drug exposure. Recall bias is low (no retrospective data collection).	non-prescription drugs are not included in the database; inpatient drug use is hardly recorded in the database; Prescription refills do not always mean medicine intake.
Confounder factors: Several confounder factors included (maternal age, confounder drug use, maternal diabetes, previous pregnancy outcomes in the last 4 years). Recall bias is low (no retrospective data collection).	No data on some potential confounders (e.g. maternal smoking, acute fever, employment status, pregnancy outcomes more than 4 years before).

The limitations of the OEP database will be balanced by the following approaches:

- In Hungary, almost all women are insured and even the uninsured women receive free healthcare services related to their pregnancy. Lack of insurance is a theoretical selection bias in general, however, in practical aspects it has marginal relevance in Hungary.
- Private healthcare services are not included in the OEP database. However, the use of private healthcare services is restricted to a small fraction of the population in Hungary.
- Pregnancy outcomes are diagnosed and reported to the OEP by medical professionals. The investigated eight pregnancy outcome categories are hard endpoints which are reliably reported to the payer's database.
- Sensitivity analyses with alternative estimates of the first day of pregnancy (±2 weeks) are planned. In addition, several time periods of pregnancy will be investigated in parallel (first trimester, first month, second month, third month, second and third month, and after the first trimester).
- Non-prescription (OTC) drugs are not supposed to have teratogenic / abortive effects, and their use is expected to be balanced between groups. However, a protective effect of some OTC drugs can not be ruled out (e.g. folic acid).
- Inpatient drug use is hardly recorded in the OEP database. However, fungal gynecologic infections are treated in the outpatient setting in most of the cases. In addition, even the inpatients are provided with a prescription instead of the prescribed product in many cases.
- Confounder factors diabetes and in vitro fertilisation are also looked for at the level of HBCS codes, which have a satisfactorily cover of inpatient interventions.
- All butoconazole, miconazole, nystatin, and metronidazole containing products in Hungary are prescription drugs, therefore patient exposure to these compounds is recorded in the OEP database (note that products not insured by OEP are less reliably

documented in the database). However, some pharmaceutical formulations of clotrimazole are non-prescription products, with the consequent lack of available patient-level exposure records in the OEP database. Accordingly, the exposure to clotrimazole will probably be underestimated both in cases and in controls. Note that all of the authorized clotrimazole products are locally administered (which do not suggest significant differences in their bioavailability). Moreover, the extent of underestimation of their use is not expected to be different across cases and controls: drug exposure records precede the pregnancy outcome and are not affected by increased awareness in cases / recall bias.

- It is acknowledged that a prescription refill do not always mean medicine intake. However, analysis of prescription refills is an acknowledged and frequently applied approach to monitor patient drug use in the real-life clinical setting. Asking the patients about their drug use would not add to the reliability of prescription refill data, because of the introduction of a substantial source of recall bias.
- Potential confounders without relevant data in the OEP database (e.g. maternal smoking, fever-related influenza or common cold, employment status, use of selected OTC drugs) will not be included in the OEP database analyses. It is not expected that these confounding factors show correlations both with the pregnancy outcomes and with the exposure to gynecology anti-infectives.
- The effect of random error is minimised by the large sample size (almost 1 100 000 pregnancy outcomes expected in the OEP database).

All together, the planned approach is considered to be suitable to give relevant answers to the research questions. A wider range of confounder factors are considered in the planned analyses than in most published studies in this field, and the planned sensitivity analyses are considered to be adequate to characterise the robustness of the study findings.

Note that all of the statistical analyses, including sensitivity analyses and confounding factors are prospectively defined in the protocol; that the study protocol will be approved by GYEMSZI and registered in the EU PAS Register before the start date of data collection; and that no pilot study was conducted on the reported pregnancy outcomes during the planning of the current study.

In the risk assessment of medicinal products on human pregnancy, there are known difficulties with the accurate documentation and validation of cases. Acknowledging the usual uncertainties in the source data, the requested number of pregnancies with prospectively collected, first trimester exposure in the relevant guideline have been inflated to 300 (to exclude a 10x risk of malformations) and to 1000 (to exclude a 2-fold risk of malformations) [EMEA/CHMP, 2008]. The current study is expected to include almost 1 100 000 pregnancy outcomes, with a conservative assumption that at least 300 pregnancies were exposed to butoconazole in the first trimester.

9.10. Other aspects

Not applicable.

10. Protection of human subjects

The current study is considered to be in the best interest of the Hungarian population. The scientific quality of the study is ensured by the internationally recognized, Company-independent Principal Investigator and by the strict regulations of PASS studies in the EU.

In the OEP database, the access to individual data will be restricted to authorized personnel, handling the data in strict confidence by their professional standards and legal obligations. No transfer of individual data from OEP will occur by any means. The results provided to the sponsor and other relevant parties will contain groups statistics and results only, without individual data.

According to the Hungarian regulation, no informed consent of the registered persons is requested in retrospective studies (23/2002 EüM rendelet, §20/Q).

11. Management and reporting of adverse events/adverse reactions

The Sponsor encourages the OEP and NIHD/OEFI to report any noticed adverse reaction, drug exposure during pregnancy, or congenital anomaly case to the competent authority, as long as this reporting procedure conforms their data management standards and regulations.

The results provided to the Sponsor and other parties will contain groups statistics and results only, without individual data. Therefore, the Sponsor can not generate new cases in the Company safety database, and hence, can not report new cases to the competent authorities from this study. Nevertheless, the final report of the study containing the results of all pre-planned analyses will be made available for the competent authorities.

12. Plans for disseminating and communicating study results

Study results will be used for regulatory correspondence (e.g. update of the Summary of Product Characteristics / Patient Information Leaflet) by the Sponsor.

The study will be registered in the EU PAS Register before the start of data collection. Protocol and final report of the study will be uploaded to the EU PAS Register.

Publication of study results is also under consideration. The Sponsor holds the right to the final review and approval of the manuscript of any publication of this study (including the final report) before publication. Authorship of approved publications will be shared across the responsible parties.

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Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1	1	02 May 2013	ENCePP checklist for study protocols

Annex 2. ENCePP checklist for study protocols

ENCePP Checklist for study protocols (Revision 2, amended) has been completed and signed by the Principal Investigator and is attached as a stand-alone document.

Annex 3. Additional information

Annex 3.1. Identification and technical definitions of pregnancy outcomes

Identification of all pregnancies / births in the OEP database

The following HBCS codes will be used to identify all pregnancies / births (i.e. the relevant mother and/or offspring TAJ numbers) in the OEP database:

HBCS code	Description (in Hungarian)
14 671A	Császármetszés
14 671B	Császármetszés pathológiás terhesség után
14 672A	Nagy rizikójú szülés (kivéve: császármetszés)
14 672B	Nagy rizikójú szülés (kivéve: császármetszés) pathológiás terhesség után
14 673A	Hüvelyi szülés
14 673B	Hüvelyi szülés pathológiás terhesség után
14 673C	Hüvelyi szülés epidurális érzéstelenítéssel
14 673D	Hüvelyi szülés pathológiás terhesség után epidurális érzéstelenítéssel
14 674A	Hüvelyi szülés műtéttel
14 674B	Hüvelyi szülés műtéttel, pathológiás terhesség után
14 675A	Genetikai amniocentézis kromoszómavizsgálattal
14 675B	Chorionboholy mintavétel kromoszómavizsgálattal
14 6760	Egyéb terhességi műtétek
14 677A	Postpartum, post abortum betegségek műtétei
14 677B	Postpartum, post abortum betegségek műtét nélkül
14 6780	Méhen kívüli (ectopias) terhesség műtétei laparoszkóppal
14 6790	Méhen kívüli (ectopias) terhesség műtétei laparotomiával
14 6800	Inkomplett vetélés műszeres befejezéssel 12 hétig
14 681C	Középidős vetélés (spontán és művi)
14 681D	Interruptio aspirációs kürettel 12. hét előtt, altatással
14 6820	Fenyegető vetélés
14 6830	Fenyegető koraszülés
14 6831	Fenyegető koraszülés kezelése Tractocile-vel, a terhesség betöltött 24. hetétől a 33. hetéig
14 6840	Egyéb antepartum betegségek
15 7110	Újszülött, születési súly 999 g alatt
15 7120	Újszülött, születési súly 1000-1499 g, jelentős műtéttel
15 7130	Újszülött, születési súly 1000-1499 g, jelentős műtét nélkül
15 7140	Újszülött, születési súly 1500-1999 g, jelentős műtéttel
15 715Z	Újszülött, születési súly 1500-1999 g, jelentős műtét nélkül, súlyos problémával
15 7160	Újszülött, születési súly 1500-1999 g, jelentős műtét nélkül, közepes problémával
15 7170	Újszülött, születési súly 1500-1999 g, jelentős műtét nélkül, egyéb problémával
15 7180	Újszülött, születési súly 2000-2499 g, jelentős műtéttel
15 719Z	Újszülött, születési súly 2000-2499 g, jelentős műtét nélkül, súlyos problémával
15 7200	Újszülött, születési súly 2000-2499 g, jelentős műtét nélkül, közepes problémával
15 7210	Újszülött, születési súly 2000-2499 g, jelentős műtét nélkül, normális újszülött diagnózissal
15 7220	Újszülött, születési súly 2000-2499 g, jelentős műtét nélkül, egyéb problémával
15 7230	Újszülött, születési súly 2499 g felett, jelentős műtéttel
15 7240	Újszülött, születési súly 2499 g felett, kisebb hasi műtéttel
15 7260	Újszülött, születési súly 2499 g felett, jelentős műtét nélkül, közepes problémával
15 7270	Újszülött, születési súly 2499 g felett, jelentős műtét nélkül, normális újszülött diagnózissal
15 7280	Újszülött, születési súly 2499 g felett, jelentős műtét nélkül, egyéb problémával
15 7300	Újszülött, áthelyezve 5 napos kor előtt, helyben született

15 7310	Újszülött, áthelyezve 5 napos kor előtt, máshol született
15 7330	Jelentős szív-érrendszeri műtétek újszülött korban
15 7331	Jelentős szív-érrendszeri műtétek újszülött korban, 5 napot meghaladó gépi lélegeztetéssel
15 7332	Jelentős szív-érrendszeri műtétek újszülött korban, 5 napot meghaladó gépi lélegeztetéssel és NO adással
15 734Z	Újszülött, születési súly 2499 g felett, jelentős műtét nélkül, súlyos problémával, 5 napot nem meghaladó gépi lélegeztetéssel
15 735Z	Újszülött, születési súly 2499 g felett, jelentős műtét nélkül, súlyos problémával, 5 napnál hosszabb gépi lélegeztetéssel

Identification of specific pregnancy outcomes in the OEP database

According to the Guideline on the Exposure to Medical Products During Pregnancy: Need for Post-Authorisation Data [EMEA/CHMP, 2005], pregnancy outcomes to be evaluated in the postmarketing phase include the following eight categories:

- ectopic pregnancy
- spontaneous abortion
- elective termination (foetal defects)
- elective termination (no foetal defects or unknown)
- stillbirth with foetal defects
- stillbirth without foetal defects
- live birth with congenital anomaly
- live birth without congenital anomaly

These mutually exclusive outcomes will be identified in the OEP database based on the following technical definitions below.

BNO codes reported as conditions in the anamnesis (if any) will not be evaluated, and BNO codes reported as potential / unconfirmed diagnoses are also excluded from the study.

Ectopic pregnancy

a) Maternal disease codes (BNO) specific for ectopic pregnancy (in Hungarian)

BNO	Description
O0000	Hasűri terhesség
O0010	Kürtterhesség (tubaris abortus)
O0020	Petefészek terhesség
O0080	Egyéb méhen kívüli terhesség
O0090	Méhen kívüli terhesség, k.m.n.

b) Offspring disease codes (BNO) specific for ectopic pregnancy (in Hungarian)

BNO	Description
P0140	Méhen kívüli terhesség

c) Intervention codes (OENO) specific for ectopic pregnancy (in Hungarian)

OENO	Description
57430	Operatio graviditatis intraabdominalis
57435	Extrauterin graviditas laparoscopos műtéte
57442	Laparoscopos embryo aspiratio, salpingotomiából
57502	Méhen kívüli terhességbe adott inj., UH vezérléssel
57503	Méhen kívüli terhességbe adott inj., laparoszkópos

d) HBCS codes specific for ectopic pregnancy (in Hungarian)

HBCS	Description
14 6780	Méhen kívüli (ectopias) terhesség műtétei laparoszkóppal
14 6790	Méhen kívüli (ectopias) terhesség műtétei laparotomiával

e) Technical definition of ectopic pregnancy in the current study

Any report of the above maternal disease (BNO) codes and/or foetal disease (BNO) codes and/or intervention (OENO) codes. *(Note that HBCS codes 14 6780 and 14 6790 do not contain additional cases, because the listed maternal disease (BNO) codes are obligatory part of them).*

In case of multiple reports in the same mother within 2 cycles (i.e. 56 days), the earliest report will be analysed and all subsequent reports within this time period will be ignored.

Spontaneous abortion

a) Maternal disease codes (BNO) specific for spontaneous abortion (in Hungarian)

BNO	Description
O0210	Missed abortion
O03	Spontán vetélés
O05	Vetélés egyéb okból
O06	Vetélés k.m.n.

Three-digit BNO codes represent all 5-digit BNO codes starting with the indicated 3 digits.

b) Offspring disease codes (BNO) specific for spontaneous abortion (in Hungarian)

BNO	Description
none	

c) Intervention codes (OENO) specific for spontaneous abortion (in Hungarian)

OENO	Description
56903	Missed ab. befejezése
56905	Curettage-incomplett abortus után

d) HBCS codes specific for spontaneous abortion (in Hungarian)

HBCS	Description
14 6800	Inkomplett vetélés műszeres befejezéssel 12 hétig

e) Technical definition of spontaneous abortion cases in the current study

Any report of the above maternal disease (BNO) codes and/or intervention (OENO) codes. *(Note that HBCS code 14 6800 does not contain additional cases, because the listed maternal disease (BNO) codes are obligatory part of this HBCS).*

In case of multiple reports of new diagnoses in the same mother within 2 cycles (56 days), the latest report will be analysed and all previous reports within this time period will be ignored.

Elective termination (foetal defects)

a) Maternal disease codes (BNO) specific for elective termination (in Hungarian)

BNO	Description
O04	Terhességmegszakitás (művi vetélés szociális vagy orvosi indikáció alapján)
Z6400	Nem kívánt terhességből adódó gondok

Three-digit BNO codes represent all 5-digit BNO codes starting with the indicated 3 digits.

b) Offspring disease codes (BNO) specific for elective termination (in Hungarian)

BNO	Description
none	

c) Intervention codes (OENO) specific for elective termination (in Hungarian)

OENO	Description
56900	Terhességmegszakítás nem orvosi indikációra
57500	Terhességmegszakítás intraamniális gyógyszerrel
57501	Terhességmegszakítás extraamniális gyógyszerrel
57510	Interruptio vacuummal
57520	Interruptio Hegar tágítással, curettage-al
57521	Interruptio laminaria tágítással
57522	Gyógyszerrel végzett interruptio befejezése
57523	Prostaglandin feltöltés, középidős vetélésinductio
57524	Rivanol (1-ezrelékes) feltöltés, középidős vetélésinductio
57525	Oxytocin infusio, középidős vetélésindukció

d) HBCS codes specific for elective termination (in Hungarian)

HBCS	Description
14 681D	Interruptio aspirációs kürettel 12. hét előtt, altatással

(Note that HBCS code 14 681D does not contain additional cases, because the listed maternal disease (BNO) codes are obligatory part of this HBCS).

e) Maternal disease codes (BNO) specific for foetal defects (in Hungarian)

BNO	Description
O3360	Veszélyeztetett terhesség téraránytalanságot okozó hydrocephalus miatt
O3370	Vesz.terhesség téraránytalanságot okozó egyéb magzati deformitás miatt
O3500	Vesz. terhesség a magzati közp.idegrendszer fejlődési rendell. miatt

f) Offspring disease codes (BNO) specific for foetal defects (in Hungarian)

BNO	Description
Q00	Agyvelőhiány és hasonló fejlődési rendellenességek
Q01	Agyvelősérv (encephalocele)
Q02	Kisfejűség
Q03	Veleszületett vízfejűség
Q04	Az agy egyéb veleszületett rendellenességei
Q05	Gerinchasadék (spina bifida)
Q06	A gerincvelő egyéb veleszületett fejlődési rendellenességei
Q07	Az idegrendszer egyéb veleszületett rendellenességei
Q10	A szemhéjak, könnyszervek és szemüreg veleszületett rendellenességei
Q11	Szemhiány, kisszemüség, nagyszemüség

Q12	A szemlencse veleszületett rendellenességei
Q13	A szem elülső szegmentjének veleszületett rendelenességei
Q14	A szem hátsó szegmentjének veleszületett rendellenességei
Q15	A szem egyéb veleszületett rendellenességei
Q16	A fül veleszületett, hallászavart okozó rendellenességei
Q17	A fül egyéb veleszületett rendellenességei
Q18	Az arc és nyak egyéb veleszületett rendellenességei
Q20	A szív üregeinek és összeköttetéseinek veleszületett rendellenességei
Q21	A szívsövények veleszületett rendellenességei
Q22	A háromhegyű és a tüdőverőér-billentyűk veleszületett rendellenességei
Q23	Az aorta- és kéthegyű billentyűk veleszületett rendellenességei
Q24	A szív egyéb veleszületett rendellenességei
Q25	A nagy artériák veleszületett rendellenességei
Q26	A nagyvénák veleszületett rendellenességei
Q27	A perifériás érrendszer egyéb veleszületett rendellenességei
Q28	A keringési szervrendszer egyéb veleszületett rendellenességei
Q30	Az orr veleszületett rendellenességei
Q31	A gége veleszületett rendellenességei
Q32	A légcső és hörgők veleszületett rendellenességei
Q33	A tüdő veleszületett rendellenességei
Q34	A légzőrendszer egyéb veleszületett rendellenességei
Q35	Szájpadhasadék
Q36	Ajakhasadék
Q37	Szájpad- ajakhasadék
Q38	A nyelv, száj és garat egyéb veleszületett rendellenességei
Q39	A nyelőcső veleszületett rendellenességei
Q40	A tápcsatorna felső szakaszának egyéb veleszületett rendellenességei
Q41	A vékonybél veleszületett hiánya, elzáródása, szűkülete
Q42	A vastagbél veleszületett hiánya, elzáródása és szűkülete
Q43	A bél egyéb veleszületett rendellenességei
Q44	Az epehólyag, epevezetékek és máj veleszületett rendellenességei
Q45	Az emésztőrendszer egyéb veleszületett rendellenességei
Q50	A petefészkek, petevezetők és széles szalagok veleszületett rendellenességei
Q51	A méh és méhnyak veleszületett rendellenességei
Q52	A női nemi szervek egyéb veleszületett rendellenességei
Q53	Nem descendált here (cryptorchismus)
Q54	Hypospadiasis
Q55	A férfi nemi szervek egyéb veleszületett rendellenességei
Q56	Határozatlan neműség és pseudohermaphroditismus
Q60	A vese agenesise és egyéb veseállomány csökkenéssel járó elváltozások
Q61	Cystás vesebetegség
Q62	A vesemedence veleszületett, elzáródást okozó rendellenességei és a húgyvezeték veleszületett malformatioi
Q63	A vese egyéb veleszületett rendellenességei
Q64	A húgyrendszer egyéb veleszületett rendellenességei
Q65	A csípő veleszületett deformitásai
Q66	A lábak veleszületett rendellenességei
Q67	A fej, arc, gerinc és mellkas csont-izomrendszerének veleszületett rendellenességei
Q68	A csont és izomrendszer egyéb veleszületett deformitásai
Q69	Számfeletti ujjak (polydactylia)
Q70	Összenőtt ujjak (syndactylia)
Q71	A felső végtag redukciós defektusai
Q72	Az alsó végtag redukciós defektusai
Q73	Nem meghatározott végtag redukciós defektusai
Q74	Egyéb veleszületett végtag-rendellenességek
Q75	Az agy- és arckoponya csontjainak egyéb veleszületett rendellenességei
Q76	A gerinc és csontos mellkas veleszületett rendellenességei
Q77	Csont-porcképződési zavar (osteo-chondrodysplasia) a csöves csontok és gerinccsontok növekedési defektusával
Q78	Egyéb osteo-chondrodysplasiák
Q79	A csont-izomrendszer m.n.o. veleszületett rendellenességei
Q80	Ichthyosis congenita
Q81	Epidermolysis bullosa
Q82	A bőr egyéb veleszületett rendellenességei
Q83	Az emlő veleszületett rendellenességei

Q84	A kültakaró egyéb veleszületett rendellenességei
Q85	Phakomatosisok, m.n.o.
Q86	Veleszületett malformatiós szindrómák ismert külső ok miatt m.n.o.
Q87	Egyéb meghatározott, több szervrendszert érintő malformatiós szindrómák
Q89	Egyéb veleszületett, m.n.o. rendellenességek

Note that maternal reports of unclear anomalies, and offspring reports of chromosomal abnormalities are not analysed in the current study (i.e. the following BNO codes are not analysed: O2830 Antenatalis szűrés során ultrahang-lelet rendellenesség; O2840 Antenatalis szűrés során radiologiai rendellenesség; O2850 Antenatalis szűrés során felfedezett chromosoma és genetikai rendell.; O2880 Antenatalis szűrés során felfedezett egyéb rendellenességek; Q90 Down-szindróma; Q91 Edwards-szindróma és Patau-szindróma; Q92 Egyéb autoszomális, m.n.o. részleges vagy teljes triszómiák; Q93 Az autoszómák m.n.o. monoszómiái és deletiói; Q95 Kiegyenlített átrendeződések és szerkezeti markerek, m.n.o.; Q96 Turner-szindróma; Q97 Egyéb szex-kromoszóma rendellenességek, női fenotipussal, m.n.o.; Q98 Egyéb szex-kromoszóma rendellenességek, férfi fenotípussal, m.n.o.; Q99 Egyéb kromoszóma rendellenességek, m.n.o.).

g) Offspring intervention codes (OENO) specific for foetal defects (in Hungarian)

OENO	Description
12660	Szívkatéterezés alapvizsgálat
12730	Szívkatéterezés, vénás percután behatolással
12731	Szívkatéterezés, vénás feltárásos behatolással
12740	Szívkatéterezés, vénás transseptális behatolással
12750	Szívkatéterezés, egyéb artériás percután behatolással
12751	Szívkatéterezés, artéria femorális behatolással
12752	Szívkatéterezés, artéria brachiális behatolással
12754	Szívkatéterezés, artériás feltárásos behatolással
12780	Szívkatéterezés-transthoracalis behatolással
50100	Punctio ventriculi cerebri, drain
50216	Cranialis meningocele és encephalocele reconstuctio
50230	Ventriculo-atrialis shunt beültetés
50240	Ventricularis shunt revisioja
50342	Spinalis meningocele és myelocele, reconstructio
50343	Extra-intr.spin.lipomával komb.meningo-myeloc.műtét
50361	Lumbo-peritonealis shunt
52174	Choanalis atresia miatt végzett műtét
52740	Szájüreg plasztikai helyreállítása
52750	Lágyszájpadplasztika
52751	Keményszájpadplasztika
52752	Kemény- és lágyszájpadplasztika, egy ülésben
52753	Szájpadrekonstrukció, előzetes műtét után
52910	Exstirpatio cystae colli lateralis
53114	Tracheostomia
53344	Hörgőfistula zárása izomlebeny plasztikával
53471	Sutura diaphragmae
53472	Reconstructio diaphragmae
53474	Reconstructio diaphragmae, alloplasticaval
53475	Duplicatio diaphragmae
53552	Defectus artef.septi interauric.cordis transvasalis
54210	Oesophagostomia cervicalis
54270	Sutura oesophagei p. cervicalis
54271	Sutura oesophagei p. thoracalis
54273	Occlusio fistulae oesophago-trachealis/bronchialis
54274	Cardioplastica
54275	Occlusio fistulae / stomae oesophagei
54541	Duodeno-duodenostomia
54543	Ductus omphaloentericus vagy residuuma eltávolítás
54550	Resectio intestini crassi
54551	Haemicolectomia dextra
54557	Resectio intestini crassi, anastomosis instrument.
54560	Colectomia
54570	Vékonybél anastomosis (bypass)
54581	Ileo-transversostomia

54590	Colo-colostomia
54687	Reconstructio malrotationis intestinorum
54853	Megacolon congenitum definitiv műtéte
54865	Magas/intermediaer recto-analis atresia def. műtéte
5486A	Rectoplastica posterior sagittalis sec.Pena
54965	Reconstr.ani definitiv., alacsony atresia ani miatt
55125	Choledocho-enterostomia
55160	Reconstr. duct. hepatici seu choledochi
55168	Choledochus-cysta eltávolítás, epeút reconstructio
55350	Reconstructio parietis abdominis
55358	Gastroschisis műtéte
55390	Hernioplastica herniae intraabdominalis
55541	Nephrectomia radicalis
55570	Pyelon plast.et res.pyeloureteralis Andersen-Hynes
55604	Ureteroendoscopos resectio
55621	Ureterotomia, alsó szakasz
55631	Ureter resectio + anastomosis
55650	Ureterocutaneostomia
55671	Anastomosis uretero-ureteralis termino-terminalis
55672	Anastomosis uretero-ureteralis latero-lateralis
55673	Revisio anastomosis ureteris
5567A	Neoimplantatio ureteris sec. Politano - Leadbetter
5567B	Neoimplantatio ureteris sec. Cohen
55784	Húgyhólyag sutura
55820	Húgycső congenitalis billentyű resectioja
55980	Ureterkatéter felvezetés
55983	Ureter strictura katéteres tágítása
55985	Ureterkatéter - dupla J - felhelyezés
56130	Scrotum és tunica vaginalis reconstructio
56240	Orchidopexia
56303	Funiculocele resectio
56310	Mellékhere cysta kiirtása
56330	Epididymectomia
56342	Funiculus és mellékhere reconstructio
56511	Ovarialis cysta eltávolítás (Bonney műtét)
58286	Syndactylia csontos szétválasztása, kézen
58400	Amputatio digiti manus
58402	Amputatio digiti manus secondarius
58450	Amputatio digiti pedis
58981	Oldalsó inkomplett ajakhasadék zárása
58982	Ajak és külső száj plastica, Le Mesurier szerint
58983	Ajak és külső száj plastica, Millard szerint
58985	Ajak- és külső szájplasztika

h) HBCS codes specific for foetal defects (in Hungarian)

HBCS	Description
none	

i) Technical definition of „elective termination (foetal defect)" cases in the current study

The following pregnancy outcomes are considered to be elective termination:

- Report of maternal disease codes (BNO) specific for elective termination, and/or
- Report of intervention codes (OENO) specific for elective termination.

The following pregnancy outcomes are considered to be „elective termination (foetal defect)":

- Elective termination as defined above, and at least one of the following in ± 3 months around the date of elective termination:

    - Report of maternal disease code (BNO) specific for foetal defect; or
    - Report of offspring disease code (BNO) specific for foetal defect; or
    - Report of offspring intervention codes (OENO) specific for foetal defect.

In case of multiple reports of elective termination (as new diagnosis) in the same mother within 2 cycles (56 days), the latest report will be analysed and all previous elective termination reports within this time period will be ignored.

Elective termination (no foetal defects or unknown)

For the tabular listing of maternal and offspring disease codes and intervention codes specific for elective termination and foetal defect, please see the definition of „Elective termination (foetal defect)" above.

The following pregnancy outcomes are considered to be „elective termination (no foetal defect or unknown)":

- Report of maternal disease codes (BNO) specific for elective termination, and/or report of intervention codes (OENO) specific for elective termination,

    without any of the following reports in ± 3 months around the date of elective termination:

    - Report of maternal disease code (BNO) specific for foetal defect; or
    - Report of offspring disease code (BNO) specific for foetal defect; or
    - Report of intervention codes (OENO) specific for foetal defect.

In case of multiple reports of elective termination (as new diagnosis) in the same mother within 2 cycles (56 days), the earliest report will be analysed and all subsequent elective termination reports within this time period will be ignored.

Stillbirth with foetal defects

a) Maternal disease codes (BNO) specific for stillbirth (in Hungarian)

BNO	Description
O3120	Továbbviselt többes terhesség magzat intrauterin elhalása után
O3640	Veszélyeztetett terhesség intrauterin elhalás miatt
O8340	Darabolásos műtét szülés kapcsán
Z3710	Egyszeres halvaszülés
Z3730	Ikerszülés: egy élve és egy halva született
Z3740	Ikerszülés: mindkettő halva született
Z3760	Többszörös ikrek szülése: néhány élve született
Z3770	Többszörös ikrek szülése, mind halva született

b) Offspring disease codes (BNO) specific for stillbirth (in Hungarian)

BNO	Description
P95H0	A magzat elhalása nem meghatározott ok miatt

c) Intervention codes (OENO) specific for stillbirth (in Hungarian)

OENO	Description
none	

d) HBCS codes specific for stillbirth (in Hungarian)

HBCS	Description
none	

e) BNO, OENO and HBCS codes specific for foetal defect (in Hungarian)
See subsections (e) to (h) at the „Elective termination (foetal defect)" definitions.

f) Technical definition of „stillbirth with foetal defect" cases in the current study

The following combinations of reports are considered to represent stillbirths with foetal defect:

- Maternal and/or offspring disease codes (BNO) specific for stillbirth, and at least one of the following in the relevant time period (from 6 months before stillbirth, up to 3 months after stillbirth):

    - Report of maternal disease code (BNO) specific for foetal defect; or
    - Report of offspring disease code (BNO) specific for foetal defect; or
    - Report of intervention codes (OENO) specific for foetal defect.

In case of both maternal and offspring reports of foetal defect, the cases will be checked against duplication in the analysis.

BNO codes reporting more than one stillbirth from the same pregnancy (Z3740, Z3770) will be handled as two stillbirth cases in the analyses.

Stillbirth without foetal defects

a) BNO, OENO and HBCS codes specific for stillbirth (in Hungarian):
see subsections (a) to (d) at the „Stillbirth with foetal defects" definitions.

b) BNO, OENO and HBCS codes specific for foetal defects (in Hungarian):
see subsections (e) to (h) at the „Elective termination (foetal defect)" definitions.

c) Technical definition of „stillbirth without foetal defects" cases in the current study

- Maternal and/or offspring disease codes (BNO) specific for stillbirth, without any of the following reports in the relevant time period (from 6 months before stillbirth, up to 3 months after stillbirth):

    - Report of maternal disease code (BNO) specific for foetal defect; or
    - Report of offspring disease code (BNO) specific for foetal defect; or
    - Report of intervention codes (OENO) specific for foetal defect.

BNO codes reporting more than one stillbirth from the same pregnancy (Z3740, Z3770) will be handled as two separate stillbirth cases in the analyses.

Live birth with congenital anomaly

a) Maternal disease codes (BNO) specific for live birth (in Hungarian)

BNO	Description
O8000	Koponyavégű, spontán hüvelyi szülés
O8010	Medencevégű hüvelyi spontán szülés
O8080	Egyéb spontán egyes szülés
O8090	Spontán egyes szülés, k.m.n.
O8100	Szülés kimeneti fogóműtéttel
O8110	Szülés üregi fogóműtéttel
O8120	Szülés üregi fogóműtéttel, a koponya forgatásával
O8130	Szülés egyéb és k.m.n. fogóműtéttel
O8140	Szülés vacuum extractióval
O8150	Szülés fogó és vacuum extractio együttes alkalmazásával
O8200	Szülés elektív császármetszéssel, k.m.n.
O8210	Szülés császármetszéssel
O8220	Szülés sürgős császármetszéssel és méheltávolítással
O8280	Egyéb egyes szülés császármetszéssel
O8290	Szülés császármetszéssel, k.m.n.
O8300	Farlehúzásos exctractio
O8310	Egyéb műfogásos szülés farfekvés esetén
O8320	Egyéb, műfogással segített szülés
O8330	Élő magzat szülése hasűri terhességben
O8380	Egyéb egyes szülés meghatározott műfogással
O8390	Egyes szülés műfogással, k.m.n.
O8400	Többes szülés, valamennyi spontán
O8401	Ikerszülés, valamennyi spontán
O8402	Hármas vagy többes szülés, valamennyi spontán
O8410	Többes szülés, valamennyi fogóval és vacuum extractorral
Z3700	Egyszeres élveszülés
Z3720	Ikerszülés
Z3730	Ikerszülés: egy élve és egy halva született
Z3750	Többszörös ikrek szülése
Z3760	Többszörös ikrek szülése: néhány élve született
Z3790	Szülés, k.m.n.

BNO codes reporting more than one live birth from the same pregnancy (Z3750, Z3760) will be handled as two stillbirth cases in the analyses.

b) Offspring disease codes (BNO) specific for live birth (in Hungarian)

BNO	Description
Z3800	Újszülött, szülés kórházban
Z3810	Újszülött, szülés a kórházon kívül
Z3820	Újszülött, egyes, születési hely, k.m.n.
Z3830	Ikerszülött, szülés a kórházban
Z3840	Ikerszülött, szülés kórházon kívül
Z3850	Ikerszülött, szülés helye, k.m.n.
Z3860	Többszörös iker, szülés a kórházban
Z3870	Többszörös ikerszülött, szülés a kórházon kívül
Z3880	Többszörös ikerszülés, szülés helye, k.m.n.

c) Intervention codes (OENO) specific for live birth (in Hungarian)

OENO	Description
57400	Császármetszés – corporalis, longitudinalis
57410	Császármetszés – cervicalis, transversalis
57420	Császármetszés - extraperitonealis
57421	Császármetszés sterilizálással

d) HBCS codes specific for live birth (in Hungarian)

HBCS	Description
15 7110	Újszülött, születési súly 999 g alatt
15 7120	Újszülött, születési súly 1000-1499 g, jelentős műtéttel
15 7130	Újszülött, születési súly 1000-1499 g, jelentős műtét nélkül
15 7140	Újszülött, születési súly 1500-1999 g, jelentős műtéttel
15 715Z	Újszülött, születési súly 1500-1999 g, jelentős műtét nélkül, súlyos problémával
15 7160	Újszülött, születési súly 1500-1999 g, jelentős műtét nélkül, közepes problémával
15 7170	Újszülött, születési súly 1500-1999 g, jelentős műtét nélkül, egyéb problémával
15 7180	Újszülött, születési súly 2000-2499 g, jelentős műtéttel
15 719Z	Újszülött, születési súly 2000-2499 g, jelentős műtét nélkül, súlyos problémával
15 7200	Újszülött, születési súly 2000-2499 g, jelentős műtét nélkül, közepes problémával
15 7210	Újszülött, születési súly 2000-2499 g, jelentős műtét nélkül, normális újszülött diagnózissal
15 7220	Újszülött, születési súly 2000-2499 g, jelentős műtét nélkül, egyéb problémával
15 7230	Újszülött, születési súly 2499 g felett, jelentős műtéttel
15 7240	Újszülött, születési súly 2499 g felett, kisebb hasi műtéttel
15 7260	Újszülött, születési súly 2499 g felett, jelentős műtét nélkül, közepes problémával
15 7270	Újszülött, születési súly 2499 g felett, jelentős műtét nélkül, normális újszülött diagnózissal
15 7280	Újszülött, születési súly 2499 g felett, jelentős műtét nélkül, egyéb problémával
15 7300	Újszülött, áthelyezve 5 napos kor előtt, helyben született
15 7310	Újszülött, áthelyezve 5 napos kor előtt, máshol született
15 7330	Jelentős szív-érrendszeri műtétek újszülött korban
15 7331	Jelentős szív-érrendszeri műtétek újszülött korban, 5 napot meghaladó gépi lélegeztetéssel
15 7332	Jelentős szív-érrendszeri műtétek újszülött korban, 5 napot meghaladó gépi lélegeztetéssel és NO adással
15 734Z	Újszülött, születési súly 2499 g felett, jelentős műtét nélkül, súlyos problémával, 5 napot nem meghaladó gépi lélegeztetéssel
15 735Z	Újszülött, születési súly 2499 g felett, jelentős műtét nélkül, súlyos problémával, 5 napnál hosszabb gépi lélegeztetéssel

Note that these HBCS codes may contain additional cases, because the listed maternal disease (BNO) codes are NOT obligatory part of most of these HBCS categories.

e) BNO, OENO and HBCS codes specific for foetal defect (in Hungarian)
See subsections (e) to (h) at the „Elective termination (foetal defect)" definitions.

f) Technical definition of „live birth with foetal defect" cases in the current study

The following pregnancy outcomes are considered to be <u>„live birth"</u> cases:

- Report of maternal disease codes (BNO) specific for live birth, and/or
- Report of offspring disease codes (BNO) specific for live birth, and/or
- Report of intervention codes (OENO) specific for live birth, and/or
- Report of HBCS codes specific for live birth.

Since the same live birth can be identified in multiple levels (maternal BNO, offspring BNO, OENO, HBCS), the above reports must be cross-linked and checked against duplicates before inclusion in the analyses.

The following pregnancy outcomes are considered to be <u>„live birth with foetal defect"</u>:

- Live birth as defined above, and at least one of the following reports in the relevant time period (from 8 months before live birth, up to 1 year after live birth):

- Report of maternal disease code (BNO) specific for foetal defect; and/or
- Report of offspring disease code (BNO) specific for foetal defect; and/or
- Report of intervention codes (OENO) specific for foetal defect.

BNO codes reporting more than one live birth from the same pregnancy (Z3720, Z3750, Z3760, Z3830, Z3840, Z3850, Z3860, Z3870, Z3880) will be handled as two live birth cases in the analyses.

Live birth without congenital anomaly

a) BNO, OENO and HBCS codes specific for live birth (in Hungarian)
See subsections (a) to (d) at the „Live birth with foetal defect" definitions.

b) BNO, OENO and HBCS codes specific for foetal defect (in Hungarian)
See subsections (e) to (h) at the „Elective termination (foetal defect)" definitions.

c) Technical definition of „live birth without congenital anomaly" cases in the current study
The following pregnancy outcomes are considered to be „live birth without foetal defect":

- Live birth as defined above, without any of the following reports in the relevant time period (from 8 months before live birth, up to 1 year after live birth):
    - Report of maternal disease code (BNO) specific for foetal defect; and/or
    - Report of offspring disease code (BNO) specific for foetal defect; and/or
    - Report of intervention codes (OENO) specific for foetal defect.

BNO codes reporting more than one live birth from the same pregnancy (Z3720, Z3750, Z3760, Z3830, Z3840, Z3850, Z3860, Z3870, Z3880) will be handled as two live birth cases in the analyses.

It is expected that all pregnancy outcomes in the OEP database will match one and only one of the investigated categories:

- ectopic pregnancy
- spontaneous abortion
- elective termination (foetal defects)
- elective termination (no foetal defects or unknown)
- stillbirth with foetal defects
- stillbirth without foetal defects
- live birth with congenital anomaly
- live birth without congenital anomaly

In cases where **none of these pregnancy outcomes** (as defined above) were reported, the pregnancy outcome will be categorized as **„Unidentified / unknown"**. The planned analysis of pregnancies without identified pregnancy outcome is detailed in Section 9.7.9.

In cases where **more than one pregnancy outcome** (as defined above) were reported for the same mother and the same pregnancy in the below specified time periods, the following hierarchy of outcome diagnoses is proposed (with the exception of BNO codes reporting twin pregnancies which are handled as two or more separate pregnancies in the analyses):

Ectopic pregnancy co-reported within 28 days with:
- spontaneous abortion, or
- elective termination (foetal defects), or
- elective termination (no foetal defects or unknown)

will be diagnosed as **ectopic pregnancy.**

Elective termination (foetal defects) co-reported within 28 days with:
- spontaneous abortion, or
- elective termination (no foetal defects or unknown)

will be diagnosed as **elective termination (foetal defects)**.

Spontaneous abortion co-reported within 28 days with:
- elective termination (no foetal defects or unknown)

will be diagnosed as **spontaneous abortion**.

Stillbirth without foetal defects reported 0 to 22 weeks later than:
- ectopic pregnancy, or
- spontaneous abortion, or
- elective termination (no foetal defects or unknown)

will be diagnosed as **stillbirth without foetal defects**.

Stillbirth with foetal defects reported 0 to 22 weeks later than:
- ectopic pregnancy, or
- spontaneous abortion, or
- elective termination (foetal defects), or
- elective termination (no foetal defects or unknown)

will be diagnosed as **stillbirth with foetal defects**.

Live birth without congenital anomaly reported 0 to 22 weeks later than:
- ectopic pregnancy, or
- spontaneous abortion, or
- elective termination (foetal defects), or
- elective termination (no foetal defects or unknown)

will be diagnosed as **live birth without congenital anomaly**.

Live birth with congenital anomaly reported 0 to 22 weeks later than:
- ectopic pregnancy, or
- spontaneous abortion, or
- elective termination (foetal defects), or
- elective termination (no foetal defects or unknown)

will be diagnosed as **live birth with congenital anomaly**.

Stillbirth with foetal defects co-reported within 22 weeks with:
- stillbirth without foetal defects

will be diagnosed as **stillbirth with foetal defects.**

Stillbirth with foetal defects co-reported within 22 weeks with:
- live birth without congenital anomaly

will be diagnosed as **live birth with congenital anomaly**.

Stillbirth with foetal defects co-reported within 22 weeks with:
- live birth with congenital anomaly

will be diagnosed as **live birth with congenital anomaly**.

Stillbirth without foetal defects co-reported within 22 weeks with:
- live birth without congenital anomaly

will be diagnosed as **live birth without congenital anomaly**.

Stillbirth without foetal defects co-reported within 22 weeks with:
- live birth with congenital anomaly

will be diagnosed as **live birth with congenital anomaly**.

Live birth with congenital anomaly co-reported within 22 weeks with:
- live birth without congenital anomaly

will be diagnosed as **live birth with congenital anomaly**.

In all of these unexpected cases with multiple reported outcomes, the diagnosed pregnancy outcome (underlined above in the listing) will be included in the analysis, while the above listed co-reported pregnancy outcomes within the specified time periods will be neglected in the analysis.

Annex 3.2. Determination of gestational age in the OEP database

Definition of the investigated time periods

According to the Guideline on the Exposure to Medical Products During Pregnancy: Need for Post-Authorisation Data [EMEA/CHMP, 2005], all studies should try to address drug exposure in specified time periods of the pregnancy:

- Before conception
- First trimester
- After first trimester
- During all pregnancy
- Unknown

Therefore, attempts are taken to separately analyse drug exposure as a potential risk factor in these time periods.

Exposure „during all pregnancy" is interpreted as exposure in both the first trimester and after the first trimester; and exposure „before pregnancy" is interpreted as exposure in the last 30 days before Day 1.

All exposed cases must be allocated to one and only one of the above categories (e.g. cases with "During all pregnancy" exposure shall not be counted at exposure in "First trimester" or "After first trimester").

Cases not exposed to the tested drug in the time period ranging from minus 30 days before Day 1 of pregnancy to the date of pregnancy outcome will be classified as „not exposed".

Determination of the first day of pregnancy in the OEP database

The first day of pregnancy is defined as the first day of the last menstrual period (LMP). This date is not included in the OEP database, therefore the first day of pregnancy is calculated back from the reported date of an obligatory investigation in pregnant women (AFP screening test after 16 completed weeks of pregnancy).

AFP screening test is reported to the OEP database as follows:

OENO code	Description (in Hungarian)
OENO 2662G	AFP meghatározása szérumban
OENO 26670	Alfa-fetoprotein meghatározása szérumban (terhes)

Based on clinical recommendations and expert consultations, biological sample collection for the AFP test in pregnancy and reporting practice to the OEP database show the following temporal pattern:

- typical period of blood sample collection for AFP screening in clinical practice: from Day 106 to Day 136 of pregnancy.

- median day of blood sample collection for AFP screening in clinical practice: Day 120 of pregnancy.

- typical delay between blood sample collection for AFP screening and reported date to OEP in a pilot analysis of 21 pregnancies across Hungary: range -2 to +30 days, mean 2.5 days, median 0 days, interquartile range 0 to +2 days. Accordingly, a 1-day delay will be assumed in the calculations.

Therefore, calculating the first day of pregnancy from the reported date of AFP screening allows a mean estimate of about 120+1=121 days with an inherent uncertainty of about ±2 weeks.

Late reports of AFP sampling were noticed in some cases (up to 30 days in a small-scale pilot analysis). Therefore, the gestational age calculated from the reported AFP date will be overwritten with an ***alternative estimate*** as follows:

Criteria of „late AFP reporting":

the reported AFP date is 97 - 150 days later than the earliest report of any pregnancy-specific condition (BNO) or intervention (OENO).

Calculation of Day 1 in cases / controls with late AFP reporting:

First day of pregnancy = the date of the earliest report of any pregnancy-specific condition/intervention, minus 30 days (the latter is the minimal gestational age at diagnosis of pregnancy).

In this context, pregnancy-specific conditions and interventions are tabulated below.

Pregnancy-specific condition (BNO) codes:

BNO	Description (in Hungarian)
O....	any BNO code starting with „O"
Z3210	Terhesség, bizonyított
Z3400	Terhesgondozás első terhesség esetén
Z3480	Terhesgondozás egyéb normális terhességben
Z3520	Terhesség problematikus és terhelő szülészeti előzményt követően
Z3590	Terhesgondozás k.m.n. veszélyeztetett terhesség esetében
Z6400	Nem kívánt terhességből adódó gondok

Pregnancy-specific intervention (OENO) codes:

OENO	Description (in Hungarian)
....	all OENO codes listed in any of the tables of Annex 3.1.
36140	Terhességi transabdominalis UH vizsgálat
36141	Terhességi transvaginalis UH vizsgálat
89611	CTG terhesség alatt (NST)
89612	CTG terheléses
94750	Terhesség alatti torna

By the introduction of the alternative estimate in late AFP reporting pregnancies, the uncertainty of AFP-based calculation of day 1 is expected to be lowered. Nevertheless, pregnancies fulfilling the criteria of „late AFP reporting" will be excluded from a sensitivity analysis (CA_sensitivity_9).

As an additional measure against the remaining uncertainty, two further sensitivity analyses are included in the protocol with alternative definitions of Day 1 of pregnancy:

analysis ID	First day of pregnancy
main analysis	{AFP reported date} minus 121 days
CA_sensitivity_1	{AFP reported date} minus (121+14) days
CA_sensitivity_2	{AFP reported date} minus (121-14) days

Relevant time period of AFP screening tests

AFP screening tests reported after the pregnancy outcome are not considered to be related to the current pregnancy.

AFP screening tests reported more than 26 weeks before the pregnancy outcome are not considered to be related to the current pregnancy. The rationale for the 26-week time period is that most births occur until the completion of gestation week 42 (i.e. not more than 26 weeks later than the earliest recommended time of AFP test).

Handling of pregnancy outcomes with 2 or more reported „AFP date" in the relevant time period

In cases with two or more reported AFP screening tests in the relevant time period, the date of the first AFP test will be taken into account (the second screening test in this time period is interpreted as a confirmatory examination).

Handling of pregnancy outcomes without reported AFP screening test in the relevant time period

- Ectopic pregnancy, spontaneous abortion, elective termination (no foetal defects or unknown): gestational age is not calculated from AFP screening test dates, because these outcomes most frequently precede the completed 16 weeks of gestation. The assumed mean gestational age in these cases is described in Section 9.7.1, together with the planned sensitivity analyses.

- Elective termination due to foetal defects: In cases without a reported AFP screening test in the relevant time period, the gestational age at elective termination will be assumed to be 14 weeks. Rationale: in Hungary, an obligatory ultrasound investigation of pregnant women is scheduled on the 12-13th weeks of pregnancy with the aim of early diagnosis of congenital anomalies. The earliest recommended time of AFP screening test is at the completion of gestational week 16. The assumed gestational age

of 14 weeks is a mean estimate of cases with diagnosed anomalies before AFP screening.

- Late pregnancy outcomes (stillbirth and live birth): cases without reported AFP screening tests in the relevant time period will be assumed to have the average gestational age of cases belonging to the same pregnancy outcome with reported AFP screening test dates.

Foetal defect / congenital abnormality cases and healthy controls without reported AFP screening test in the last 26 weeks before pregnancy outcome are excluded from a sensitivity analysis (CA_sensitivity_4) of the teratogenicity case-control study.

Annex 3.3. Case-control study of spontaneous abortions in the OEP database

Annex 3.3.1. Scientific background

According to the terminology of the Guideline on the Exposure to Medical Products During Pregnancy: Need for Post-Authorisation Data, spontaneous abortions are characterised by early foetal death before 22 completed weeks of pregnancy (note that late foetal death after 22 completed weeks of pregnancy is referred to as stillbirth) [EMEA/CHMP, 2005].

Spontaneous abortions in the first 4-5 weeks of pregnancy usually remain unnoticed or are appearing as a slightly delayed and slightly more intensive menses. Accordingly, the exact frequency of spontaneous abortions can not be measured. As a rough estimate, 65-70% of all conceptions are followed by spontaneous abortion (including the symptom-free cases), and about 70% of all spontaneous abortions occur in the first trimester [Papp Z, 1999].

The rate of diagnosed spontaneous abortion among wanted and diagnosed pregnancies is about 15-20% [Papp Z, 1999].

The largest published study of drugs approved for the treatment of vaginitis (miconazole, clotrimazole, nystatin, candicidin, aminacrine, metronidazole) as risk factors for spontaneous abortion was a large-scale case-control study based on the Michigan Medicaid dataset, including pregnancy outcomes and prescription claims [Rosa FW, 1987]. The study was limited to the time period of 1980 – 1983, and butoconazole was unfortunately not included in this analysis. The study compared the rate of spontaneous abortions to the rate of normal deliveries (with similar gestational age at the comparison), and also to the rate of legal abortions, in separate analyses. Clotrimazole and miconazole exposure in the preceding 120-day period increased the risk of spontaneous abortion (clotrimazole RR = 1.36, 95% CI 1.1 – 1.6; miconazole RR = 1.38, 95% CI 1.2 – 1.5) versus normal delivery, whereas large numbers of exposures to nystatin and aminacrine compounds did not show this association, suggesting that spontaneous abortions are caused by the imidazole agents clotrimazole and miconazole rather than the condition being treated. However, as an alternative explanation, the protecting effect of nystatin and aminacrine against a confounding effect of the treated condition theoretically can not be ruled out. Metronidazole exposure was also associated with an increased relative risk of spontaneous abortion vs. normal delivery (RR = 1.67, 95% CI 1.4 – 2.0). Regarding the comparisons of spontaneous and legal abortion rates, the authors argued that the use of drugs not recommended in pregnancy (like metronidazole) is biased toward more use before planned legal abortions, therefore these comparisons are less easier to interpret [Rosa FW, 1987]. The definition of cases, normal delivery controls and drug exposure in the Rosa study are summarized below:

	Definition of cases	Definition of controls	Drug exposure criteria
Rosa 1987 [Rosa FW, 1987]: Michigan Medicaid, 1980-1983			
main analysis	spontaneous abortions (ICD9-634-634.9) in the database (N = 4264)	inpatient deliveries with at least 180-day history in the database (only the first delivery of each women in the evaluated period) (N = 55 736)	Rx in a 120-day period before spontaneous abortion; Rx in a 120 day period, ending 180 days before delivery.
sensitivity analysis	spontaneous abortions (ICD9-634-634.9), with at least one Medicaid-reimbursed service 70-250 days before spontaneous abortion *(to exclude spontaneous abortions with insufficient medical history in the database)*, and without delivery diagnosis within 6 months after spontaneous abortion *(to exclude imminent / incipient abortions)* (N = 2326)	inpatient deliveries: with at least one Medicaid-reimbursed service 270-450 days before delivery *(to exclude pregnancies with insufficient medical history in the database)*, only the first delivery of each women in the evaluated period (N= 32 944)	Rx in a 120-day period before spontaneous abortion; Rx in a 120 day period, ending 200 days before delivery.

In the Rosa study, potential confounding factors (indication, obesity, diabetes) were mentioned but not included in the statistical analysis of spontaneous abortion risk factors.

In other studies, the most important confounding variables considered were maternal age [Chan RL, 2010; Davanzo J, 2012; Gissler M, 2010; Gray RH, 2000; Howards PP, 2012; Nakhai-Pour HR, 2010; Nakhai-Pour HR, 2011; Nybo Andersen AM, 2000; Roman E, 1992; Small CM, 2007; Sozio J, 1998], and history of previous spontaneous abortions [Chan RL, 2010; Gray RH, 2000; Nakhai-Pour HR, 2011; Nybo Andersen AM, 2000; Roman E, 1992; Sozio J, 1998]. Other confounding factors were occasionally also included in some studies, including e.g. maternal education [Chan RL, 2010; Davanzo J, 2012; Roman E, 1992], alcohol use [Chan RL, 2010; Gray RH, 2000; Howards PP, 2012; Roman E, 1992], current smoking [Clark CA, 2011a; Gray RH, 2000; Howards PP, 2012; Roman E, 1992; Sozio J, 1998], maternal infertility [Small CM, 2007], maternal chronic conditions [Nakhai-Pour HR, 2010; Nakhai-Pour HR, 2011], or the use of medications suspected of increasing the risk of spontaneous abortion. Examples for the latter are nonaspirin NSAIDs [Clark CA, 2011a; Nakhai-Pour HR, 2011] and antidepressants evaluated by ATC groups [Nakhai-Pour HR, 2010]. Place of residence [Davanzo J, 2012; Gissler M, 2010; Roman E, 1992] and calendar effect (in 5-10 year blocks) was also evaluated in some studies [Davanzo J, 2012; Gissler M, 2010; Nybo Andersen AM, 2000].

Regarding the relevant drug exposure time period before spontaneous abortion, the identified studies show substantial heterogenity (see below).

Study reference	Drug exposure criteria
[Rosa FW, 1987]	in 120 days before index date
[Gissler M, 2010]	0-3 months before pregnancy

[Nakhai-Pour HR, 2011]	from Day 1 to index date; in 60 days before index date; in 14 days before index date
[Nakhai-Pour HR, 2010]	from Day 1 to index date; in 30 days before index date
[Howards PP, 2012]	in 12 weeks before index date, or: {from day minus 28 to day 91 (4 weeks before pregnancy + 13 completed weeks} (kétféle adatlap)

Accordingly, the main analysis in the current study follows the Rosa study [Rosa FW, 1987], while the planned sensitivity analyses will focus on shorter drug exposure periods (60 days and 30 days before index date). For the list and technical definitions of the selected confounder parameters, please see Annex 3.3.2.

Annex 3.3.2. Technical definitions related to spontaneous abortion cases

Evidence of exposure to drug substances in the relevant time periods will be evaluated in a dichotomous way (yes/no). Any OEP-recorded prescription refill will be handled as evidence of exposure. The following active substances will be analysed:

Gynecology anti-infectives
butoconazole
miconazole
clotrimazole
metronidazole (local)
metronidazole (systemic)
nystatin
Non-aspirin NSAIDs
diclofenac
naproxen
any NSAID

Drug-drug combination medicinal products containing any of the listed active ingredients will be included in the analysis.

Maternal age at index date will be categorized in 5-year groups, handled as a nominal parameter.

In addition, the following confounder factors will be considered, integrated into a single propensity score:

- Evidence of previous spontaneous abortion(s)
  - YES:
    - history of BNO codes specific for spontaneous abortion in the last 4 years before index date (not including the current pregnancy outcome): *O0210, O03, O05, O06, N96H0, O2620, Z3510* (3-digit BNO codes represent all 5-digit BNO codes starting with the indicated 3 digits), and/or
    - history of OENO codes specific for spontaneous abortion in the last 4 years before index date (not including the current pregnancy outcome): *56903, 56905 ;* and/or
    - report of BNO *N96H0, O2620, or Z3510* in the current pregnancy.
  - NO:
    - lack of evidences specified above

- Evidence of previous elective abortion(s)
  - YES:
    - history of BNO codes specific for elective termination in the last 4 years before index date: *O04, Z6400* (3-digit BNO codes represent all 5-digit BNO codes starting with the indicated 3 digits), and/or
    - history of OENO codes specific for elective termination in the last 4 years before index date: *56900, 57500, 57501, 57510, 57520, 57521, 57522, 57523, 57524, 57525.*
  - NO:
    - lack of evidences specified above

- Evidence of previous live birth:
  - YES:
    - maternal history of BNO codes *Z3480, Z3540* and/or *any BNO code starting with „O"* (except for *O8340*) in the last 4 years before index date; and/or
    - maternal history of intervention codes (OENO) in the last 4 years before index date: *57400, 57410, 57420, 57421 ;* and/or
    - maternal history of HBCS codes specific for live birth in the last 4 years before index date: *15 7110, 15 7120, 15 7130, 15 7140, 15 715Z, 15 7160, 15 7170, 15 7180, 15 719Z, 15 7200, 15 7210, 15 7220, 15 7230, 15 7240, 15 7260, 15 7270, 15 7280, 15 7300, 15 7310, 15 7330, 15 7331, 15 7332, 15 734Z, 15 735Z.*
  - NO:
    - lack of evidences specified above

- Evidence of infertility treatment in the last 4 years:
  - YES:
    - maternal history of BNO codes in the last 4 years before index date: *N9880, N9890, Z3110, Z3120, Z3130, Z3140, Z3500;* and/or
    - maternal history of intervention OENO codes in the last 4 years before index date: *14703, 16944, 92700, 92701, 92722, 97722, 97723, 97724;* and/or
    - maternal history of HBCS codes in the last 4 years before index date: *13 6530, 13 6540, 13 6550, 13 6560.*
  - NO:

- lack of evidences specified above

- Evidence of more than one foetus in current pregnancy
  - YES:
    - report of maternal BNO codes in the last 120 days before index date: *O3000, O3010, O3020, O3080, O3090, O3110, O3120, O3180, O3250, O3260, O6610, O8400, O8401, O8410, O8411, O8412, O8420, O8421, O8422, O8490, O8491, O8492 Z3720, Z3730, Z3740, Z3750, Z3760, Z3770, Z3830, Z3840, Z3850, Z3860, Z3870, Z3880,* and/or
    - report of intervention OENO codes in the last 120 days before index date: *57526, 57527.*
  - NO:
    - lack of evidences specified above

- Evidence of maternal diabetes
  - YES: at least two reports as specified below, separated by at least 30 days, in the last 4 years before pregnancy or during pregnancy:
    - maternal history of BNO codes: *O2400, O2410, O2420, O2430, O2440, O2490; and/or*
    - maternal history of intervention OENO codes: *89010, 89843, 91312, 91313, 91314, 91316, 91317, 91318, 91319, 91320, 91321;* and/or
    - maternal history of prescription refill for drugs belonging to ATC A10.
  - NO:
    - lack of evidences specified above

- year of index date
  - nominal parameter, values from 2005 to 2011.

- month of index date
  - nominal parameter, values from January to December

Annex 3.4. Case-control study of teratogenic risk in the OEP database

Annex 3.4.1. Scientific rationale

Definition of cases and controls

The intention of the study is to evaluate the total (birth + foetal) risk of congenital anomalies in the offspring of mothers who were exposed to the tested drugs. Accordingly, the group of „cases" is defined in this analysis as the pooled group of the following pregnancy outcomes:

- Elective termination (foetal defects)
- Stillbirth with foetal defects
- Live birth with congenital anomaly

The control group in the main analysis consists of live births without congenital anomaly, similarly to previous studies [Acs N, 2009b; Acs N, 2010; Czeizel AE, 1998; Kazy Z, 2005; Nelson MM, 1971], but without matching to confounding factors (see below). In some sensitivity analyses, the control group will be defined as the pooled group of all live births and stillbirths without congenital anomaly / foetal defect [Rosa FW, 1987].

All pregnancy outcomes in these analyses will be identified as provided in Annex 3.1.

In addition, the following sensitivity analyses are planned, to test the robustness of the results:

Planned analyses of spontaneous abortions	
Main analysis	
• Cases = Elective termination (foetal defects), Stillbirth with foetal defects, Live birth with congenital anomaly. • Controls = Live birth without congenital anomaly • Day 1 of pregnancy = {AFP reported date} minus 121 days; in pregnancies with late AFP reports an alternative Day 1 estimate will be applied (as specified in Annex 3.2.).	
Alterations from the main analysis in sensitivity analyses	
CA_sensitivity_1*	Day 1 of pregnancy = {AFP reported date} minus 135 days
CA_sensitivity_2*	Day 1 of pregnancy = {AFP reported date} minus 107 days
CA_sensitivity_3*	Controls = live births without congenital anomaly, stillbirths without foetal defect
CA_sensitivity_4*	Cases and controls without reported AFP screening test in the last 26 weeks before pregnancy outcome are excluded from the analysis
CA_sensitivity_5*	Cases = Stillbirth with foetal defects, Live birth with congenital anomaly.
CA_sensitivity_6*	Cases = Elective termination (foetal defects), Stillbirth with foetal defects, Live birth with congenital anomaly, restricted to cases with at least one of the following anomalies / interventions reported in the offspring:

	BNO Q35 cleft palate BNO Q36 cleft lip BNO Q37 cleft lip, cleft palate OENO 52750 Lágyszájpadplasztika OENO 52751 Keményszájpadplasztika OENO 52752 Kemény- és lágyszájpadplasztika, egy ülésben OENO 52753 Szájpadrekonstrukció, előzetes műtét után OENO 58981 Oldalsó inkomplett ajakhasadék zárása OENO 58982 Ajak és külső száj plastica, Le Mesurier szerint OENO 58983 Ajak és külső száj plastica, Millard szerint OENO 58984 Ferde archasadék (macrostoma) korrekciója OENO 58985 Ajak- és külső szájplasztika OENO 58986 Ajakkorrekció ajakplasztika után OENO 58987 Median ajakhasadék zárása
CA_sensitivity_7*	Cases = Elective termination (foetal defects), Stillbirth with foetal defects, Live birth with congenital anomaly, restricted to cases with at least one of the following anomalies / interventions reported in the offspring: BNO Q7920 exomphalos BNO Q7930 gastroschisis BNO Q7940 prune belly syndrome BNO Q7950 other congenital anomalies of the abdominal wall OENO 55340 Hernioplastica umbilicalis OENO 55350 Reconstructio parietis abdominis OENO 55358 Gastroschisis műtéte OENO 55359 Omphalocele műtéte OENO 55360 Reconstructio parietis abdominis c. implant. OENO 55361 Reconstructio laparoscopica parietis abdominis cum implantate OENO 55369 Reconstructio laparoscopica parietis abdominis cum conversione
CA_sensitivity_8*	Cases = Live birth in 2005, with foetal defect / congenital anomaly reported until the end of 2012. Controls: Live birth in 2005, foetal defect / congenital anomaly NOT reported until the end of 2012.
CA_sensitivity_9	Cases and controls fulfilling the criteria of any alternative estimation of Day1 of pregnancy (see in Annex 3.2.) are excluded.

** In pregnancies with late AFP reports an alternative Day 1 estimate will be applied, as specified in Section 9.7.2. and Annex 3.2.*

Rationale for these sensitivity analyses:

Sensitivity analyses 1, 2, 4, and 9 intends to deal with the uncertainty of the calculation of the first day of pregnancy.

Sensitivity analyses 6 and 7 focus on those congenital anomalies reported in preclinical tests with butoconazole (in a single species, at high doses only): cleft palate, and abdominal wall defects, respectively [FDA Label Information, 2003].

Sensitivity analyses 3 and 5 provide alternative definitions of controls and cases, respectively, to test the robustness of the results.

Sensitivity analysis 8 deals with possible late diagnoses / late reports of congenital anomalies.

Time periods of drug exposure

In this analysis, drug exposure in the following periods will be evaluated:
- first trimester [Nelson MM, 1971; van Gelder MM, 2011]
- first month (before organogenesis) [Acs N, 2009b; van Gelder MM, 2011]
- second month[Czeizel AE, 1999; van Gelder MM, 2011]
- third month[Czeizel AE, 1999; van Gelder MM, 2011]
- second and third month (the critical period for congenital anomalies) [Acs N, 2009b; Banhidy F, 2007; Czeizel AE, 1999; Kazy Z, 2005]
- after the first trimester [Acs N, 2009b; Kazy Z, 2005]

Confounding factors

In most epidemiological studies, the problem of confounding adds to the uncertainty in conclusions drawn. This is also true for studies on the effect of maternal drug use on birth defect risks. Different methods exist for the control of confounder factors. In a case-control study, this can be done by matching when the controls to cases are selected with, for instance, the same maternal age and other characteristics one wants to adjust for. More common, notably when large datasets are analysed, is to adjust for the confounders in the statistical analysis. The most common way to do this is by using a logistic regression model [Kallen B, 2012].

In a recent series of population-based large-scale case-control studies on drug-induced congenital abnormalities in the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) 1980-1996, the following confounding factors have been considered [Acs N, 2009b; Acs N, 2010]:

Confounding factor	Adjustment method
sex	matched controls
birth week in birth year	
district of parent's residence	
maternal age *(<20year / 20-29year / >29year)*	adjusted odds ratio
birth order *(first delivery / second or more)*	
maternal employment status *(professional-managerial-skilled worker / semi-skilled worker-unskilled worker-housewife / others)*	
fever related influenza and/or common cold *(yes / no)*	
acute maternal diseases of digestive system *(yes / no)*	
other drugs *(yes / no)*	

folic acid use *(yes / no)*	

The most consistently considered confounders in studies of other datasets were maternal age at delivery [Kazy Z, 2005; Nelson MM, 1971; van Gelder MM, 2011] and parity (number of previous live births) [Kazy Z, 2005; Nelson MM, 1971; van Gelder MM, 2011]. In addition, the van Gelder study included a wide range of additional confounder factors, typically as binary parameters (history of miscarriages, history of induced abortions, history of stillbirths, pre-pregnancy BMI higher than 25, maternal education >12 years, fever during gestational weeks 0–12, smoking during gestational weeks 0–12, and folic acid use from 4 weeks before pregnancy through week 8 of gestation [van Gelder MM, 2011]. Note that there is no available data from the OEP database on some of these potential confounders. Pre-existing diabetes was an exclusion criteria in the van Gelder study, therefore the present study also considers the potential confounding effect of diabetes (see in Annex 3.4.2.).

Some potential confounding factors including maternal employment status, folic acid use, maternal education, and smoking can not be controlled for in the present analysis, because of the lack of adequate data in the OEP database.

Pre-pregnancy body mass index neither can be controlled for in this analysis, because of the lack of adequate data in the OEP database. The mechanism behind the effect of obesity is unclear and a possible explanation is that obesity is associated with an increased risk of diabetes type 2 [Kallen B, 2012]. The current study will adjust the calculated risks to the confounding effect of diabetes.

The district of the mother's permanent residence is coded in Hungary in a 4-digit system, with around 3600 nominal values. Therefore, this parameter is not included in the regression model. Instead, place of residence will be categorized as „village" or „town" in all of the counties.

The indication treated is not expected to be a confounding factor in the analysis of congenital anomalies, because none of the investigated vaginal candidiasis drugs was associated with increased risk of congenital anomalies in the Rosa study [Rosa FW, 1987]. Accordingly, the treated indication itself is not considered to be a confounding factor of teratogenic risk in the present study.

The selected confounding factors with their technical definitions are provided in Annex 3.4.2.

To adjust for the confounder(s) in the statistical analysis, a logistic regression model will be applied, as recommended in a recent review on the problem of confounding in studies of the effect of maternal drug use on pregnancy outcome [Kallen B, 2012]. The logistic regression model is a regression method to predict outcome (e.g. rate of congenital malformations) as influenced by one or more confounding factors. Logistic regression is used in analyses aiming at risk determinations in a dichotomous situation, for example, presence or absence of a malformation [Kallen B, 2012].

For all analyses, odds ratio with 95% confidence intervals will be calculated (both as crude and adjusted values) as shown below. Separate tables will be presented for the main analysis and for all sensitivity analyses.

Variable	Controls N=	Cases N=	OR (95% CI)		
			crude	adjusted (1)	adjusted (2)
Type of gynecology anti-infectives					
none	N (%)	N (%)	1.00	1.00	1.00
Butoconazole					
butoconazole in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
butoconazole in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
butoconazole in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
butoconazole in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
butoconazole in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
butoconazole after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Miconazole					
miconazole in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Clotrimazole					
clotrimazole in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
clotrimazole in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
clotrimazole in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
clotrimazole in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
clotrimazole in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
clotrimazole after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Nystatin					
nystatin in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Metronidazole (local administration)					
metronidazole in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Metronidazole (systemic administration)					
metronidazole in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Maternal age at index date					
15-19 years	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
20-24 years	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
25-29 years	N (%)	N (%)	1.00	1.00	1.00
30-34 years	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)

35-39 years	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
40-45 years	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)

(1) adjusted for other drug exposure (as listed in the table) in the same pregnancy period, and for maternal age;
(2) in addition, also adjusted for all other investigated confounder factors (the latter have been integrated into a single propensity score before adjustment).

Annex 3.4.2. Technical definitions related to the analysis of teratogenicity

Exposure to gynecology anti-infectives in the relevant time periods

- butoconazole (yes/no)
- miconazole (yes/no)
- clotrimazole (yes/no)
- metronidazole (local) (yes/no)
- metronidazole (systemic) (yes/no)
- nystatin (yes/no)

Maternal age at delivery (in 5-year intervals, as a nominal parameter)

Confounding variables as integrated into a single „propensity score":

- Evidence of previous live birth
    - YES: any of the following reports in the last 4 years before Day 1 of the current pregnancy:
        - maternal history of BNO codes *Z3480, Z3540* and/or *any BNO code starting with „O"* (except for *O8340*);
        - maternal history of intervention codes (OENO): *57400, 57410, 57420, 57421;*
        - maternal history of HBCS codes specific for live birth: *15 7110, 15 7120, 15 7130, 15 7140, 15 715Z, 15 7160, 15 7170, 15 7180, 15 719Z, 15 7200, 15 7210, 15 7220, 15 7230, 15 7240, 15 7260, 15 7270, 15 7280, 15 7300, 15 7310, 15 7330, 15 7331, 15 7332, 15 734Z, 15 735Z.*
    - NO:
        - lack of evidences specified above

- Evidence of previous spontaneous abortion
    - YES: any of the following reports in the last 4 years before Day 1 of the current pregnancy:
        - history of BNO codes specific for spontaneous abortion: *O0210, O03, O05, O06, N96H0, O2620, Z3510* (3-digit BNO codes represent all 5-digit BNO codes starting with the indicated 3 digits);
        - history of OENO codes specific for spontaneous: *56903, 56905.*
    - NO:
        - lack of evidences specified above

- Evidence of maternal diabetes
    - YES: at least two reports as specified below, separated by at least 30 days, in the last 4 years before pregnancy or during pregnancy:
        - maternal history of BNO codes: *O2400, O2410, O2420, O2430, O2440, O2490; and/or*
        - maternal history of intervention OENO codes: *89010, 89843, 91312, 91313, 91314, 91316, 91317, 91318, 91319, 91320, 91321;* and/or
        - maternal history of prescription refill for drugs belonging to ATC A10.
    - NO:
        - lack of evidences specified above

- evidence of acute infection / inflammatory disease during the first trimester of pregnancy
    - YES: any of the following reports in the first trimester:
        - BNO codes: *A00 – A49, A83-A87, J00-J22, O23, O98 (3-digit BNO codes represent all 5-digit BNO codes starting with the indicated 3 digits); and/or*
        - intervention OENO codes: *19108, 19131, 19141, 19142, 19170, 19190, 19191, 19192, 19193, 25062, 25063, 25064, 25065, 25067, 25068, 25069, 25072, 25077, 25078, 25092, 25096, 25098, 25110, 25111, 25120, 25131, 25191, 25203, 25211, 25212, 25213, 25214, 25215, 25216, 25217, 25218, 25219, 25220, 25250, 25251, 25310, 25311, 25312, 25321, 25390, 25400, 25410, 25430, 25450, 25460, 25470, 25500, 25504, 25550, 25560; and/or*
        - prescription refill for drugs belonging to ATC *A07A, S01A, and/or M01A*.
    - NO:
        - lack of evidences specified above

- year of birth
    - nominal parameter, values from 2005 to 2011.

- month of birth
    - nominal parameter, values from January to December