PASS information

Title	Butoconazole use in pregnancy: population-based case-control studies on adverse pregnancy outcomes in Hungary (study protocol RGD-77425).
Version identifier of the final study report	Version 1.0
Date of last version of the final study report	21th November 2016
EU PAS register number	ENCEPP/SDPP/4282; web link to study record: http://www.encepp.eu/encepp/viewResource.htm?id=12924
Active substance	butoconazole (test drug); clotrimazole, miconazole, nystatin, metronidazole (therapeutic controls); celecoxib, diclofenac, ibuprofen, indomethacin, naproxen, rofecoxib; carbamazepine, isotretinoin, lithium, valproic acid (active controls and confounding factors).
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. To evaluate the effect of butoconazole and clotrimazole on birthweight.
Country(-ies) of study	Hungary
Author	János G. Pitter MD, PhD Syreon Research Institute Kft. 119 Thököly street, Budapest 1146, Hungary

Marketing authorisation holder(s):

Marketing authorisation holder(s)	Gedeon Richter Plc. 19-21 Gyömrői út, Budapest 1103, Hungary phone: +36 1 432 7433 email: horvathbea@richter.hu
MAH contact person	Beáta Horváth MD, PhD

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SIGNATURE PAGE

Study title: „Butoconazole use in pregnancy: population-based case-control studies on adverse pregnancy outcomes in Hungary (study protocol RGD-77425)"

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

The study was conducted in compliance with the specifications of the study protocol (final version: 8th July 2013; protocol amendment 1: 9th July 2014; protocol amendment 2: 17 July 2015), and the regulatory approval letter.

Budapest, 21th November 2016

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Nándor Ács MD, PhD, med habil

Principal Investigator

1. Abstract

Title: FINAL REPORT: Butoconazole use in pregnancy: population-based case-control studies on adverse pregnancy outcomes in Hungary (study protocol RGD-77425). Abstract, dated 5th July 2016, author: János G. Pitter MD, PhD

Keywords: butoconazole, clotrimazole, pregnancy, safety

Rationale and background: Vaginal yeast carriage is more frequent in pregnancy and increases with increasing periods of gestation. 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.

Research question and objectives: The study had two co-primary objectives: to evaluate butoconazole treatment as a potential teratogenic risk factor and as a potential risk factor of spontaneous abortion in a population-based case-control study in Hungary, based on the database of the National Healthcare Fund (OEP). Secondary objectives included the evaluation of other gynecology anti-infectives (clotrimazole, miconazole, nystatin, metronidazole) as risk factors in the same setting; to evaluate active control drugs in both analyses to assess the sensitivity of the study; 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); and to evaluate the role of butoconazole and clotrimazole in the risk of low birthweight (<2500g).

Study design: retrospective analysis of prospectively collected data in the OEP database, in case-control studies (for congenital anomalies and spontaneous abortion) and in a cohort study with quasi- randomization (for low birthweight).

Setting: all pregnancies and births in Hungary reported to the National Healthcare Fund between 01 January 2005 and 31 December 2011 (inclusive).

Subjects and study size, including dropouts: the analyses cover 790,592 women with 1,098,789 identified pregnancies, including 493 535 live births.

Variables and data sources: all variables on drug exposure, pregnancy outcomes, time periods, and confounding factors were determined based on solely the OEP database records.

Results: The co-primary analyses did not suggest an increased risk with butoconazole. Secondary analyses revealed that clotrimazole has safety advantages over butoconazole in the first trimester, while butoconazole may be the preferred anti-fungal drug from the safety point of view after week 16 of pregnancy.

Discussion: This study was the first to identify pregnancy outcomes, pregnancy time periods, and drug safety in pregnancy in a population-level study in Hungary, solely based on OEP database records. The developed methodology was validated with active controls and may support further research on the investigation of drug safety research questions in pregnancy. Due to reproductive toxicity in animals, butoconazole is currently contraindicated in Hungary in the first trimester of pregnancy and also in women of childbearing potential, unless adequate contraception is used. Based on our study, it is recommended to maintain the contraindication of butoconazole in the first trimester of pregnancy.

Marketing Authorisation Holder(s): Gedeon Richter Plc.

Names and affiliations of principal investigators: Nándor Ács MD, PhD, med. habil., Second Department of Obstetrics and Gynecology, Semmelweis University, School of Medicine, Budapest, Hungary

2. List of abbreviations

Table 2.A. List of abbreviations

95% CI	95% confidence interval
AFP	Alpha-fetoprotein
ATC	Anatomical Therapeutic Chemical classification system
BMI	Body Mass Index
BNO	The Hungarian adaptation of the ICD classification system
CA	Congenital anomaly
CHMP	Committee for Medicinal Products for Human Use
DOT	Days of therapy
EMEA	European Medicines Evaluation Agency
ENCePP Checklist	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EP	Ectopic pregnancy
ET	Elective termination without foetal defect
ET_FD	Elective termination with foetal defect
EU PAS register	European Post-authorization study register
FDA	Food and Drug Administration
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
HBCS	Diagnosis Related Groups (DRG) used for inpatient care financing in Hungary
HCAR/ HCCSCA	Hungarian Congenital Abnormality Registry / Hungarian Case-Control Surveillance of Congenital Abnormalities databases
ICD	International Classification of Diseases
LB	Live birth without cong. anomaly
LB FD	Live birth with cong. anomaly
LMP	Last menstrual period
MAH	Marketing Authorization Holder
N	Number
NHIF	National Health Insurance Fund
NIHD /OEFI	National Institute for Health Development / Országos Egészségfejlesztési Intézet
NSAID	Non-steroidal anti-inflammatory drugs
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
OR	Odds ratio
OTC	Over the Counter
PASS	Post-authorization safety study
PL/SQL	Procedural Language/Structured Query Language
PUPHA	Public Database of Reimbursable Medicines in Hungary
Rx	drug prescription
SA	Spontaneous abortion
SB	Stillbirth without foetal defect
SB_FD	Stillbirth with foetal defect
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. Investigators

Principal investigator:	Nándor Ács MD, PhD, med. habil. Second Department of Obstetrics and Gynecology, Semmelweis University, School of Medicine, Budapest, Hungary

4. Other responsible parties

The study was 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). In Protocol Amendment 2, two additional partners have joined the research team: Syreon Research Institue Ltd. (responsible for the preparation of protocol amendment 2 and the final report), and Gábor Kovács MD, PhD (paediatric expert of Syreon Research Institute). The contract with the National Institute for Health Development has been terminated before study completion and could not be extended due to the shortage of research capacity at NIHD at present.

Table 4.A. Responsible parties

Name	Address	Responsibilities	Contact person
Gedeon Richter Plc.	19-21 Gyömrői út, 1103 Budapest, Hungary	Study sponsorship,	Beáta Horváth MD, PhD Head of Unit, Strategic Analysis Unit, Medical Strategy and

		study planning and financing, project management.	Coordination Department, Gedeon Richter Plc. 32 Gyömrői út, Budapest 1103, Hungary. phone: +36 1 432 6418 email: horvathbea@richter.hu
RxTarget Kft.	10 Bacsó Nándor út 5000 Szolnok, Hungary	Participation in study planning and reporting, programming data analysis, OEP correspondence.	György Rokszin MD. CEO, RxTarget Ltd. 10 Bacsó Nándor út, Szolnok 5000, 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. Research contract terminated before 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
Prof. Zoltán Vokó, and Prof. Zoltán Kaló	ELTE Társdadalomtudományi Kar, H-1518 Budapest, Pf. 32 Building B, 1/A Pázmány Péter sétány, 1117 Budapest, Hungary	Zoltán Vokó is a professor of Epidemiology; Zoltán Kaló is a consultant Expert in clinical research. They participated in study planning and in protocol amendments, and in drawing	Prof. Zoltán Vokó Eötvös Lóránd University, Institute of Economics, Health Economics Research Centre

		conclusions in the final report.	
Syreon Research Institute Kft.	65/A Mexikói út, 1142 Budapest, Hungary	Writing of protocol amendment 2 and the final report.	János G. Pitter MD, PhD Principal researcher, Syreon Research Institute Ltd. Phone: +36 20 454 7887 Email: janos.pitter@syreon.eu
Gábor Kovács MD, PhD	65/A Mexikói út, 1142 Budapest, Hungary	Participation in the planning of Protocol Amendment 2 and in drawing conclusions in the final report.	Gábor Kovács MD, PhD Senior researcher, paediatrician, Syreon Research Institute Ltd. Phone: +36 70 430 4644 Email: gabor.kovacs@syreon.eu

5. Milestones

Planned and actual date of study milestones are detailed in Table 5.A.

Table 5.A. Planned and actual dates of study milestones

Milestone	Planned date	Actual date	Comments
Final study protocol	8 July 2013	8 July 2013	-
Submission for GYEMSZI-OGYI approval	10 July 2013	12 July 2013	-
Registration in the ENCEPP E-Register of Studies	10 July 2013	July 2013	Updated at protocol amendments
Date of GYEMSZI-OGYI approval	9 September 2013	29 October 2013	Delay in study protocol approval
Start of data collection (OEP)*	10 September 2013	20 January 2014	-
Start of data analysis and statistics	01 November 2013	10 February 2014	-
Study protocol – Amendment 1	(not planned)	09 July 2014	Protocol Amendment 1
Amendment 1, submission for GYEMSZI-OGYI approval	(not planned)	16 July 2014	
Amendment 1, date of GYEMSZI-OGYI approval	(not planned)	21 August 2014	
Study protocol – Amendment 2	(not planned)	17 July 2015	Protocol Amendment 2
Amendment 2, submission for GYEMSZI-OGYI approval	(not planned)	17 August 2015	
Amendment 2, date of GYEMSZI-OGYI approval	(not planned)	16 October 2015	
End of data collection (OEP)*	30 October 2013 / 9 June 2014 / 30 June 2015**	01 June 2016	Delay in study conduct and reporting due to two protocol amendments
End of data analysis and statistics	15 January 2014 / 31 August 2014 / 31 August 2015**	01 June 2016	
Final report of study results	15 March 2014 / 15 October 2014 / 31 December 2015**	21 November 2016	

*: start and stop date of secondary use of existing data (database research); **planned milestones in the original protocol / protocol amendment 1 / protocol amendment 2, respectively.

6. 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, 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 et al., 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, 1988; Rosa et al., 1987).

Gedeon Richter Plc is the marketing authorization holder (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.

6.1. 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, 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 factors summarized in Table 6.A.

Table 6.A. Non-clinical reproductive toxicity data on butoconazole.

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 were 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).

6.2. 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 (Gedeon_Richter_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).

6.3. 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 was 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 #31}. 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.

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

This was 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 intended 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 was also planned on the risk of spontaneous abortion in butoconazole-exposed pregnancies (first human data in this respect).

The study investigated multiple anti-infective gynecology products in the same setting, allowing a comparative assessment of the butoconazole results. (Previous comparative studies of gynecologic anti-infectives had 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 et al., 2009a; Acs et al., 2009b; Acs et al., 2010; Banhidy et al., 2007; Banhidy et al., 2011a; Banhidy et al., 2011b; Banhidy et al., 2011c; Czeizel et al., 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 were 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) did not contain any case with recorded butoconazole exposure (official statement from NIHD based on current HCAR / HCCSCA data search (National_Institute_for_Health_Development, 2013a)). Therefore, the current study was based on the National Health Insurance Fund Administration Database (OEP database). This was the first

study with the intention to determine pregnancy outcomes, pregnancy periods, drug exposure, pregnancy risks and confounding factors solely from the OEP database. The proposed, OEP-based approach may be useful also for the investigation of pregnancy risks of other drugs authorised after 1996.

A low birthweight preventive effect of clotrimazole treatment against vaginal candidiasis have been described previously (Banhidy et al., 2009; Czeizel et al., 2004; Czeizel et al., 2007). Our study was the first attempt to compare butoconazole and clotrimazole in this respect.

7. Research question and objectives

The study had 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 have been estimated 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 need to be evaluated together to allow for robust conclusions. Any positive finding in these analyses shall be interpreted in the context of similar findings with therapeutic comparators and with active control drugs. Nevertheless, in line with the co-primary objectives, two co-primary effect measueres were estimated:

- the adjusted* odds ratio in the main analysis**of foetal defect/congenital abnormality in pregnancies exposed to butoconazole in the first trimester (vs. not exposed pregnancies) (Section 9.7.10.). In case the 95% CI does not include the value 1.00, a statistically significant evidence for altered risk of teratogenicity is inferred.

  *Odds ratio adjusted for: maternal age, local miconazole / systemic miconazole / clotrimazole / local nystatin /systemic nystatin / local metronidazole / systemic metronidazole and/or systemic carbamazepine / systemic isotretinoin / local isotretionin / systemic lithium / systemic valproic acid 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, calendar effect (year and month). In Amendment 2 analyses, the propensity score also includes the socioeconomic status of the maternal residence at micro-region level, and urban /rural status, beyond the previously included variables.

  **In amendment 2 analyses, the primary endpoint refers to the “al1” EUROCAT definition of congenital anomalies.

- the adjusted*** odds ratio of spontaneous abortion in pregnancies exposed to butoconazole (vs. not exposed pregnancies). In case the 95% CI does not include the value 1.00 in the main analysis, a statistically significant evidence for altered risk of spontaneous abortion risk is inferred.

  ***Odds ratio adjusted for: maternal age, local miconazole / systemic miconazole / clotrimazole / local nystatin / systemic nystatin / local metronidazole / systemic metronidazole and/or local diclofenac / systemic diclofenac / local naproxen / systemic naproxen / celecoxib / local ibuprofen / systemic ibuprofen / rofecoxib / local indomethacin / systemic indomethacin 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). In Amendment 2 analyses, the propensity score also includes the socioeconomic status of the maternal residence at micro-region level, and urban/rural status, beyond the previously included variables.

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 evaluate active control drugs in both analyses to assess the sensitivity of the study;
- 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);
- to evaluate the role of butoconazole and clotrimazole in the risk of low birthweight (<2500g, or <2000g).

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

8. Amendments and updates

The study protocol has been amended twice. The original protocol did not match the transient and permanent social security numbers of the investigated children, resulting in the loss of medical follow-up of about 440 000 live births. In addition, the exact hierarchy of rules for redundance removal and rules to solve conflicting outcomes has not been defined in the original protocol, making outcome determination ambiguous in cases with multiple outcome records. Accordingly, the study protocol has been amended (Amendment 1).

The results as calculated by Amendment 1 indicated an unexpectedly high rate of congenital anomalies both in drug exposed and unexposed pregnancies, reflecting the oversensitive definition of congenital anomalies in this protocol version. Dilution of true congenital anomalies by false positive hits decreases the study sensitivity. Therefore, the main purpose of Amendment 2 was to introduce more restrictive definitions of congenital anomalies. Another aim was an in-depth analysis of apparent drug effects on low birthweight risk.

A detailed listing of protocol amendments is provided below (Table 8.A)

Table 8.A. Overview of protocol amendments / updates.

No.	Date	Section of study protocol	Amendment or update	Reason
1	09th July 2014	Cover page	Sponsor contact person changed	n.a.
1	09th July 2014	Section 3	Additional abrevations added to the list	Double-check of the text
1	09th July 2014	Section 3.	Sponsor contact person changed	n.a.
1	09th July 2014	Section 4.	Protocol approval date added	Caused delay in study procedures
1	09th July 2014	Section 5.	Amendment 1 summarized	Protocol amendment
1	09th July 2014	Section 6.	Timelines updated	Delay in study approval and procedures
1	09th July 2014	Section 8.	Active control drugs introduced also in the teratogenicity case-control study Myconazole systemic and local products will be analysed separately. Nystatin systemic and local products will be analysed separately.	Potential confounders, measures of study sensitivity. Miconazole systemic products are also available in Hungary. Nystatin systemic products are also available in Hungary.

No.	Date	Section of study protocol	Amendment or update	Reason
			"Evidence of acute infection / inflammatory disease in the first trimester" is deleted NSAID drugs to be investigated are listed by name	This confounding factor cannot be identified and investigated. List of the investigated NSAID products missing from the original protocol
1	09th July 2014	Section 9.2.	Children without mother records are excluded	Maternal drug exposure without identified mother can not be analysed.
1	09th July 2014	Section 9.3.	HCAR/HCCSCA sentence deleted; Active control drugs introduced in the teratogenicity assessment; Nystatin systemic and local products will be analysed separately. NSAID drugs to be investigated are listed by name	HCAR/HCCSCA records are not analysed in this study. Active control drugs are potential confounders and measures of study sensitivity; Nystatin systemic products are also available in Hungary. List of the investigated NSAID products missing from the original protocol
1	09th July 2014	Section 9.5.	Children without mother records are excluded	See above
1	09th July 2014	Section 9.7.	Two alternative analyses (according to the amendment, and according to the original protocol)	Check the sensitivity of the results to the amended methodology.
1	09th July 2014	Section 9.7.2.	NSAID drugs to be investigated are listed by name, Reference to the list of NSAID drugs; Myconazole systemic and local products will be analysed separately. Nystatin local and systemic products evaluated separately.	List of the investigated NSAID products missing from the original protocol; Miconazole systemic products are also available in Hungary. Nystatin systemic products are also available in Hungary.
1	09th July 2014	Section 9.7.9.	Active control drugs added	See above

No.	Date	Section of study protocol	Amendment or update	Reason
			NSAID drugs to be investigated are listed by name	List of the investigated NSAID products missing from the original protocol
1	09th July 2014	Section 9.7.10.	Active control drugs added; Myconazole systemic and local products will be analysed separately. Nystatin local and systemic products evaluated separately. Isotretinoin local and systemic products evaluated separately "Evidence of acute infection / inflammatory disease during the first trimester of pregnancy" is deleted	See above Miconazole systemic products are also available in Hungary. Nystatin systemic products are also available in Hungary Isotretinoin local and also systemic products are available in Hungary. This confounding factor cannot be identified and investigated
1	09th July 2014	Section 9.7.11.	Myconazole systemic and local products will be analysed separately. Nystatin local and systemic products evaluated separately.	Miconazole systemic products are also available in Hungary. Nystatin systemic products are also available in Hungary
1	09th July 2014	Section 9.9.	Further limitations and considerations added	All limitations shall be discussed in the final report.
1	09th July 2014	Annex 3.1.	Sub-sections added (Annexes 3.1.1 – 3.1.3.)	See at the subsections below.
1	09th July 2014	Annex 3.1.1.	Additional pregnancy identification approaches introduced	In addition to HBCS codes, additional approaches are also introduced to identify most of the pregnancies / births.
1	09th July 2014	Annex 3.1.2.	Additional BNO/OENO codes specific to pregnancy outcomes have been identified; Reference to updated redundance / outcome hierarchy rules in Annex 3.1.3.	Double-check of the relevant codes; See Annex 3.1.3.
1	09th July 2014	Annex 3.1.3.	Updated redundance / outcome hierarchy rules, with specific criteria of multiple	Systematic review and update, with more specific rules and logical check. For

No.	Date	Section of study protocol	Amendment or update	Reason
			outcomes from the same pregnancy.	justifications, please see the imputed text.
1	09th July 2014	Annex 3.2.	Pregnancy-specific codes added	Pregnancy-specific codes are used for pregnancy identification and for alternative Day 1 estimate in case "late AFP criteria" are fulfilled.
1	09th July 2014	Annex 3.3.2.	NSAID drugs to be investigated are listed by name and ATC codes. Additional BNO/OENO codes added to the confounding factors' criteria.	List of NSAID products missing from the original protocol; Double-check of the relevant codes.
1	09th July 2014	Annex 3.4.	Planned analysis of teratogenic risk	Typing error
1	09th July 2014	Annex 3.4.1.	Active control drugs added; two alternative analyses (according to the amendment, and according to the original protocol)	See above
1	09th July 2014	Annex 3.4.2.	Nystatin systemic and local products will be analysed separately. Active control drugs introduced also in the teratogenicity case-control study. ATC codes were added Additional BNO/OENO codes added to the confounding factors' criteria. BNO, OENO and prescriptional ATC codes for the identification of "Evidence of acute infection / inflammatory disease during the first trimester of pregnancy" are deleted	Nystatin systemic products are also available in Hungary Active control drugs are potential confounders and measures of study sensitivity; ATC codes missing from the original protocol Double-check of the relevant codes. This confounding factor cannot be identified and investigated. Acute infections are usually treated by the GP. The mentioned codes are under-documented by the GP to the OEP database

No.	Date	Section of study protocol	Amendment or update	Reason
2	17 July 2015	Title page	Date of last version updated; Active controls listed as active substances	administrative update; harmonization of title page with the document
2	17 July 2015	Title page	Additional research objective: To evaluate the effect of butoconazole and clotrimazole on birthweight.	Amendment 1 results raised additional research questions as explained in Annex 3.5.
2	17 July 2015	3. Responsible parties	Syreon Research Institute and Gábor Kovács MD, PhD added; NIHD cooperation stopped	Research capacity reasons from Gedeon Richter and NIHD side
2	17 July 2015	4. Abstract	Additional research objective: To evaluate the effect of butoconazole and clotrimazole on birthweight. Quasi-randomized study design, with logistic regression models. Birth weight will be analysed both as a binary (low / normal birthweight) and as a continuous variable.	Amendment 1 results raised additional research questions. Rationale and study design are detailed in Annex 3.5.
2	17 July 2015	5. Amendments and updates	Amendment 2 details summarized	Protocol amendment 2
2	17 July 2015	6. Milestones	Date of "end of data collection", "end of data analysis and statistics", and of "final report" have been updated	Additional data and time requirements of planning and conducting Amendment 2 analyses
2	17 July 2015	8. Research questions and objectives	Inclusion of active controls in the adjusted regression model for testing of the formal hypothesis on teratogenic risk has been clarified	Harmonization with Section 9.7.10. and with Annex 3.4.
2	17 July 2015	8. Research questions and objectives	In Amendment 2 congenital anomaly and spontaneous abortion analyses, the propensity score will also include the socioeconomic status of the maternal residence at micro-region	Efforts to correct for socioeconomic factors in Amendment 2 analyses

No.	Date	Section of study protocol	Amendment or update	Reason
			level, and urban /rural status, beyond the previously included variables.	
2	17 July 2015	8. Research questions and objectives	In amendment 2 analyses, the primary endpoint refers to the "a11" EUROCAT definition of congenital anomalies.	The a11 definition is the most inclusive of the multiple alternative congenital anomaly definitions in Amendment 2
2	17 July 2015	8. Research questions and objectives	Secondary objective added: to evaluate the role of butoconazole and clotrimazole in the risk of low birthweight (<2500g).	Amendment 1 results raised additional research questions. Rationale and study design are detailed in Annex 3.5.
2	17 July 2015	9.1 Study design	Design summary added for the Amendment 2 birthweight analyses	Amendment 1 results raised additional research questions. Rationale and study design are detailed in Annex 3.5.
2	17 July 2015	9.3 Variables	Time periods of pregnancy: risk of low birthweight will be evaluated for first trimester, second trimester, third trimester, and during pregnancy drug exposures.	Beyond first trimester exposures, drug exposure in 2nd and 3rd trimester will also be considered.
2	17 July 2015	9.3 Variables	Drug exposures: the analyses will consider drug exposure as a quantitative parameter (number of DOTs)	Amendment 1 analyses evaluated drug exposure as a binary (yes/no) variable. Drug exposure as a numeric variable will allow more graded conclusions
2	17 July 2015	9.5 Study size	Power calculations for code groups of congenital anomalies have been added to the protocol, and summarized here.	Selection of EUROCAT and custom code groups to be analysed. For justifications, see Annex 3.1.4.
2	17 July 2015	9.7 Data analysis	Logistic regression models on low birthweight has been added, with a quasi-randomized design.	Amendment 1 results raised additional research questions. Rationale and study design are detailed in Annex 3.5.
2	17 July 2015	9.7 Data analysis	Results will be reported according to Amendment 1 and Amendment 2	Experience accumulating from ongoing data collection and analysis revealed that the original study protocol failed to identify most mother –

No.	Date	Section of study protocol	Amendment or update	Reason
				offspring pairs. Moreover, pregnancy outcomes were ambiguous in cases with multiple outcome records. Accordingly, the study will not be analysed as planned in the original protocol.
2	17 July 2015	9.7 Data analysis	Overview of planned Amendment 2 changes added	For congenital anomaly analyses, see Annex 3.4.3. For spontaneous abortion analyses, see Annex 3.3.3. For birthweight analysis changes, see Annex 3.5.
2	17 July 2015	9.7 Data analysis	Schematic flowchart of the planned analyses: quasi-randomised study on low birthweight added.	Amendment 1 results raised additional research questions. Rationale and study design are detailed in Annex 3.5.
2	17 July 2015	9.7.2 Spontaneous abortions	Drug exposure: changed from binary to numeric in Amendment 2 analyses	Drug exposure as a numeric variable will allow more graded conclusions
2	17 July 2015	9.7.2 Spontaneous abortions	Crude OR: univariate analyses	clarification of crude odds ratios
2	17 July 2015	9.7.2 Spontaneous abortions	Additional analyses of spontaneous abortion risk have been introduced by Protocol Amendment 2. For details, please see Annex 3.3.3.	Reference to a new section describing the Amendment 2 changes
2	17 July 2015	9.7.8. Live births without congenital anomaly	Add descriptive statistics (mean and SD) on pregnancy duration	To check the credibility of the calculated pregnancy periods
2	17 July 2015	9.7.9. Summary table of pregnancy outcomes	The Summary Table of Pregnancy Outcomes table will be filled both according to Protocol Amendment 1 and Protocol Amendment 2 definitions.	Protocol amendment 2

No.	Date	Section of study protocol	Amendment or update	Reason
2	17 July 2015	9.7.9. Summary table of pregnancy outcomes	Layout of the table changed: additional columns for all exposed cases, and for all cases.	Exposition periods are not mutually exclusive (e.g. “during all pregnancy” cases included also in “first trimester” cases)
2	17 July 2015	9.7.10. Multivariate analysis of drug induced risk of congenital anomalies	Time profile of reporting congenital anomalies after birth: codes belonging to any of the new, alternative CA code groups will be analysed in Amendment 2	Change in definition of congenital anomaly code groups
2	17 July 2015	9.7.10. Multivariate analysis of drug induced risk of congenital anomalies	Time profile of reporting congenital anomalies: births in 2005 will be followed	Typing error in table (2004)
2	17 July 2015	9.7.11. Analysis of birth weight	Additional analyses of low birthweight have been introduced by Protocol Amendment 2. For details, please see Annex 3.5.	Reference to a new section describing the Amendment 2 changes
2	17 July 2015	9.9 Limitations of the research methods	Dilution by high numbers of minor congenital anomalies or irrelevant consitions (e.g. congenital dysplasia of the hip) added as a limitation	Amendment 1 analyses showed a high proportion of minor anomalies among the identified “congenital anomaly” cases
2	17 July 2015	9.9 Limitations of the research methods	Non-relevant codes are intended to be excluded from the analysis of teratogenicity risk by Protocol Amendment 2.	Amendment 1 analyses showed a high proportion of minor anomalies among the identified “congenital anomaly” cases
2	17 July 2015	9.9 Limitations of the research methods	Study results will be reported both per Protocol Amendment 1 and Protocol Amendment 2.	Protocol amendment 2

No.	Date	Section of study protocol	Amendment or update	Reason
2	17 July 2015	9.9 Limitations of the research methods	Limitations of the birthweight analyses in Protocol Amendment 2 are discussed in Annex 3.5.	Reference to a new section describing the Amendment 2 changes
2	17 July 2015	13. References	References added in Amendment 2	Update of reference list
2	17 July 2015	Annex 1. List of stand-alone documents	ENCEPP checklist update and a MS Excel file "Socioeconomic status of micro-regions.xlsx" added	Protocol amendment 2
2	17 July 2015	Annex 3.1.2. Identification of pregnancy outcomes in the OEP database	Code groups listings: clarification added that these definitions partly do not apply for the Amendment 2 analyses	Alternative definitions introduced in Amendment 2
2	17 July 2015	Annex 3.1.4.	Protocol Amendment 2 changes in the identification of pregnancy outcomes: exclusion of mild cases; exclusion of outpatient cases in sensitivity analyses; analysis by code subgroups. Description and justification of the selected 34 alternative CA code groups to be analysed in Amendment 2	Alternative definitions along the EUROCAT recommendations introduced in Amendment 2, to correct for the unexpectedly high rate of apparent CA cases in Amendment 1 analyses. For details and justifications, see Annex 3.1.4.
2	17 July 2015	Annex 3.2. Determination of gestational age in the OEP database	Allocation of cases to pregnancy exposure periods is not mutually exclusive. E.g. mothers with „During all pregnancy" exposure shall also be counted at exposure in „First trimester" and „After first trimester", and shall be included in the case-control analyses of all relevant exposure periods.	To avoid the fragmentation of patient groups exposed in the critical time periods

No.	Date	Section of study protocol	Amendment or update	Reason
2	17 July 2015	Annex 3.3.1. Scientific background – SA analyses	Results will be reported according to Amendment 2 (main analysis) and also according to Amendment 1 (ancillary analysis)	Protocol amendment 2
2	17 July 2015	Annex 3.3.1. Scientific background – SA analyses	Potential confounders added with references (paternal age, paternal smoking)	Updated listing of potential confounders
2	17 July 2015	Annex 3.3.3. Amendment 2 changes in SA analyses	In the regression models of the main analysis and all sensitivity analyses, binary (yes/no) drug exposure variables are replaced by numeric drug exposure variables (days of therapy). This change is consistently applied for butoconazole as well as for all therapeutic controls and active controls; The propensity score will also include the socioeconomic status of the maternal residence at micro-region level, and rural/urban status of maternal residence, beyond the currently included variables. Pregnancies with maternal age <15 years or maternal age >45 years are excluded from the Amendment 2 analyses.	Drug exposure as a numeric variable will allow more graded conclusions. Efforts to correct for socioeconomic factors in Amendment 2 analyses. Outlier maternal ages most probably reflect invalid data in the OEP database, according to RxTarget experience.
2	17 July 2015	Annex 3.4.1. Scientific background – CA analyses	Results will be reported according to Amendment 2 (main analysis) and also according to Amendment 1 (ancillary analysis)	Protocol amendment 2
2	17 July 2015	Annex 3.4.1. Scientific	Crude OR: univariate analyses	clarification of crude odds ratios

No.	Date	Section of study protocol	Amendment or update	Reason
		background – CA analyses		
2	17 July 2015	Annex 3.4.3.1. Changes in the logistic regression model of CA risk	Pregnancies with maternal age <15 years or maternal age >45 years are excluded from the Amendment 2 analyses (for justification, please see Annex 3.3.3); In the regression models of the main analysis and all sensitivity analyses, binary (yes/no) drug exposure variables are replaced by numeric drug exposure variables (days of therapy). This change is consistently applied for butoconazole as well as for all therapeutic controls and active controls; The propensity score will also include the socioeconomic status of the maternal residence at micro-region level (see in Annex 3.6), and urban/rural status of maternal residence beyond the currently included variables.	Outlier maternal ages most probably reflect invalid data in the OEP database, according to RxTarget experience. Drug exposure as a numeric variable will allow more graded conclusions. Efforts to correct for socioeconomic factors in Amendment 2 analyses.
2	17 July 2015	Annex 3.4.3.2. Definition of cases and controls	In the Amendment 2 analyses of congenital anomalies, 34 alternative definitions will be applied to cases and controls, driven by EUROCAT guidelines and expected power calculations.	Alternative definitions along the EUROCAT recommendations introduced in Amendment 2, to correct for the unexpectedly high rate of apparent CA cases in Amendment 1 analyses. For details and justifications, see Annex 3.1.4.
2	17 July 2015	Annex 3.4.3.3. Sensitivity analyses	For each alternative definition of cases and controls, 1 main analysis and 8 sensitivity analyses will apply: for 3 alternative estimates of day 1 of pregnancy, combined with the inclusion, or the exclusion	Sensitivity analyses intend to allow robust conslusions on pregnancy period exposures, and to fine-tune the apparent congenital anomaly rates in the overall population.

No.	Date	Section of study protocol	Amendment or update	Reason
			of isolated or all outpatient reports.	
2	17 July 2015	Annex 3.5 Amendment 2 changes in the analysis of low birthweight	A quasi-randomised design is introduced, with the exclusion of pregnancies exposed to butoconazole or clotrimazole prescriptions of non-gynecologists and gynaecologists with inhomogenous prescription patterns.	The rationale behind this patient population restriction is that different patient characteristics within the doctor's practice could underlie patient-specific drug selection decisions in non-homogenous prescription practices
2	17 July 2015	Annex 3.5 Amendment 2 changes in the analysis of low birthweight	Potential between-practice differences in patient characteristics are intended to be controlled for by the inclusion of the following socio-economic proxies in the logistic regression models: micro-regional development status of the maternal residence (as determined in Annex 3.6); urban / rural status of maternal residence.	To adjust for potential between-practice differences in socioeconomic status
2	17 July 2015	Annex 3.5 Amendment 2 changes in the analysis of low birthweight	Pre-defined logistic regression models and results table outline for the main analysis and for sensitivity analyses	To correct for the potential confounding effect of the included variables; Sensitivity analyses for robust conclusions.
2	17 July 2015	Annex 3.5 Amendment 2 changes in the analysis of low birthweight	Descriptive statistics will be provided on selected measurable patient characteristics, for patient groups with different socioeconomic status	To check the comparability of butoconazole and clotrimazole exposed pregnancies within the same socioeconomic subgroups

No.	Date	Section of study protocol	Amendment or update	Reason
2	17 July 2015	Annex 3.6 Socioeconomic status of micro-regions in Hungary	Maternal residence postal codes are linked to micro-regional socioeconomic status through the name of the corresponding town / village, following the official categories of deprivement status in the relevant time period.	Efforts to correct for socioeconomic factors in Amendment 2 analyses.

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 was planned, to avoid the time-consuming process of building a pregnancy registry prospectively. The study included three set of case-control analyses with a range of pre-defined confounding factors and sensitivity analyses. For a brief overview, please see the Table below. For more details, please see the indicated Sections of the report.

Table 9.A. Overview of study design

Cases	Controls	Database	Drug exposure	Report section
spontaneous abortions	live births	OEP, 2005-2011.	120 days before index date [Index date in cases: date of spontaneous abortion; index date in controls: 180 days before live birth.]	Section 10.4.1 and 15.2
foetal defects and congenital anomalies	live births without congenital anomaly	OEP, 2005-2011.	1st month, 2nd month, 3rd month, 2nd+3rd month, first trimester, after first trimester	Section 10.4.2 and 15.3
live births with weight <2500g	live births with weight ≥2500g	OEP, 2005-2011.	First trimester, second trimester, third trimester, during pregnancy	Section 10.4.3 and 15.4

Rationale to select the case-control design (instead of a retrospective cohort study): the case-control study design represents 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's effect on pregnancy outcomes in the OEP database, first the pregnancy outcome and its 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 has been registered in the EU PAS register (registration number EUPAS4282) before the start of data collection, and the final report will also be submitted to this registry.

9.1.1. Design of the spontaneous abortion case-control study

9.1.1.1. 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) (1).

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 (2). The rate of diagnosed spontaneous abortion among wanted and diagnosed pregnancies is thought to be about 15-20% (2).

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 (3). 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 exposure 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 (3). The definition of cases, normal delivery controls and drug exposure in the Rosa study are summarized in Table 9.B.

Table 9.B. Study design of the Michigan Medicaid 1980-1983 spontaneous abortion case-control study (3)

	Definition of cases	Definition of controls	Drug exposure criteria
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 woman 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 woman 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 (4-14), and history of previous spontaneous abortions (4-6, 8, 9, 11). Other confounding factors were occasionally also included in some studies, including e.g. maternal education (4, 7, 9), alcohol use (4, 8, 9, 13), current smoking (6, 8, 9, 13, 15, 16), maternal infertility (14), maternal chronic conditions (11, 12), or the use of medications suspected of increasing the risk of spontaneous abortion. Examples for the latter are nonaspirin NSAIDs (11, 15) and antidepressants evaluated by ATC groups (12). Place of residence (7, 9, 10) and calendar effect (in 5-10 year blocks) were also evaluated in some studies (5, 7, 10). Further potential confounders include paternal age above 40 years (16) or paternal smoking (17).

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

Table 9.C. Drug exposure windows in published studies on sponatenous abortion risk.

Study reference	Drug exposure criteria
(3)	in 120 days before index date
(10)	0-3 months before pregnancy

(11)	From the first day of pregnancy to index date; in 60 days before index date; in 14 days before index date
(12)	From the first day of pregnancy to index date; in 30 days before index date
(13)	Version 1: in 12 weeks before index date; Version 2: 4 weeks before pregnancy + 13 completed weeks.

Accordingly, the main analysis in the current study follows the Rosa study (3), while the planned sensitivity analyses 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 Section 9.1.1.3.

9.1.1.2. Amendment 1 study design

The Amendment 1 analysis of spontaneous abortions followed the methods described by Rosa et al (3) for clotrimazole, miconazole, nystatin and other gynecology anti-infectives with modifications detailed in Tables 9.D. and 9.E.

Table 9.D. Amendment 1 SA models, main analysis

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 of Protocol Amendment 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 of Protocol Amendment 1.
index date	in cases, reported date of spontaneous abortion; in controls, reported date of live birth minus 180 days.
drug exposure criteria	Prescription claims (Rx) in the first trimester defined as a 120-day period before index date. Amendment 2 analyses: number of prescribed doses (numeric); Amendment 1 analyses: 0 / at least 1 prescriptions (binary).

Table 9.E. Amendment 1 SA models, sensitivity analyses

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 Section 9.8.2 at the criteria of „late AFP reporting" pregnancies.*

The main analysis and the sensitivity analyses in Ammendment 1 included the following test variables:

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

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

- Exposure to non-aspirin NSAIDs within the drug exposure period
  - diclofenac (local) (yes/no)
  - diclofenac (systemic) (yes/no)
  - naproxen (local) (yes/no)
  - naproxen (systemic) (yes/no)
  - celecoxib (yes/no)
  - ibuprofen (local) (yes/no)
  - ibuprofen (systemic) (yes/no)
  - rofecoxib (yes/no)
  - indomethacin (local) (yes/no)
  - indomethacin (systemic) (yes/no)

The analyses also took efforts to consider other confounding variables, integrated into an appropriate „propensity score". For details and justifications, please see Annex 3.3 of Protocol

Amendment 1. 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) were not included in the models because of the lack of adequate data in the OEP database. However, it is not expected that these factors are associated with both the pregnancy outcome and drug exposure (15).

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 need to 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 was applied, as recommended in a recent review on the problem of confounding in studies of the effect of maternal drug use on pregnancy outcome (18). The logistic regression model is a regression method used to study the effect of an exposure of interest on the risk of an outcome conditional on one or more confounding factors in case-control studies. (18).

9.1.1.3. Amendment 1 technical definitions

Evidence of exposure to drug substances in the relevant time periods was evaluated in a dichotomous way (yes/no). Any OEP-recorded filled prescription will be handled as evidence of exposure. Active substances analysed are listed in Table 9.F.

Table 9.F. ATC codes belonging to the investigated drugs.

Gynecology anti-infectives	ATC codes
butoconazole	G01AF15
miconazole (local)	G01AF04, D01AC20; G01AF20
miconazole (systemic)	A01AB09
clotrimazole	G01AF02, D01AC01
metronidazole (local)	G01AF01; D06BX01; G01AF20
metronidazole (systemic)	P01AB01, J01XD01
nystatin (local)	G01AX
nystatin (systematic)	A07AA02
Non-aspirin NSAIDs	ATC codes
diclofenac (local)	M02AA15, S01BC03, S01CC01
diclofenac (systemic)	M01AB05, M01AC, M01AB55
naproxen (local)	M02AA12, S01CC01
naproxen (systemic)	M01AE02
celecoxib	M01AH01, L01XX33
ibuprofen (local)	M01AE01, M02AA13
ibuprofen (systemic)	M01AE01, M01AE51, C01EB16
rofecoxib	M01AH02
indomethacin (local)	M02AA23, S01BC01

indomethacin (systemic)	M01AB01

Note that products contraindicated for gynecology use were not included (see Section 9.8.3). Drug-drug combination medicinal products containing any of the listed active ingredients were included in the analysis. Maternal age at index date was categorized in 5-year groups, handled as a nominal parameter. In addition, the following confounders were 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, O3110, 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, 5744A, 5744B, 57500, 57501, 57510, 57520, 57521, 57522, 57523, 57524, 57525, 57526, 57527.
  - NO:
    - lack of evidences specified above

- Evidence of previous live birth:
  - YES:
    - history of BNO, OENO and HBCS codes specific for live birth (for listing, see Protocol Amendment 1 Annex 3.1.2.) in the last 4 years before index date; and/or
    - any offspring TAJ number recorded in the OEP database belonging to the same mother, in the last 4 years before index date.
  - 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: N9710, N9720, N9780, N9790, 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 BNO codes in the last 120 days before index date: O3000, O3010, O3020, O3080, O3090, O3110, O3120, O3180, O3250, O3260, O6610, O8400, O8401, O8402, O8410, O8411, O8412, O8420, O8421, O8422, O8480, O8481, O8482, O8490, O8491, O8492, P0150, P5030, P5050, 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 filled prescription 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

9.1.1.4. Changes introduced by Protocol Amendment 2

Amendment 1 results did not indicate significant increase in risk of spontaneous abortions in butoconazole exposed pregnancies (neither in the main analysis, nor in the pre-planned sensitivity analyses). Moreover, a significant protective effect of butoconazole was found in sensitivity analyses 2 and 5. A protective effect of exposure to locally applied metronidazole, miconazole, and nystatin products was also found in a subset of the pre-planned analyses. The most consistent protective effect was found for clotrimazole, both in the main analysis and in the pre-planned sensitivity analyses.

Interestingly, the exposure of patients to clotrimazole and butoconazole showed different time patterns. In the main analysis, we investigated drug exposure in a 120-day period before spontaneous abortion / index date and found 20388 pregnancies exposed to clotrimazole and 5466 pregnancies exposed to butoconazole. When the investigated exposure period was narrowed to the last 30 days of the same 120-day period (in sensitivity analysis 2), the number of butoconazole exposed pregnancies decreased proportionally, to about ¼ of the exposure in the main analysis

(1269 pregnancies). In contrast, the number of clotrimazole exposed pregnancies remained disproportionally high (10154 pregnancies, ~ 50% of exposure in the last 120 days). This difference in exposure pattern raises the possibility that clotrimazol receiving patients tended to fill more than one prescriptions within the investigated 120-day period. If this was the case, the apparent advantage of clotrimazole could be due to more frequent dosing, i.e. better / longer-term control of fungal vaginal infecions. As alternative explanations, more frequent dosing may be a surrogate of e.g. higher compliance, better socioeconomic status, or recurrent infections (the latter would not explain the advantage of clotrimazole).

To investigate the role of dosing frequency in the protective effect of locally administered gynecologic anti-infectives, Protocol Amendment 2 replaced the binary (yes/no) parameters of drug exposure in the spontaneous abortion regression models with appropriate numeric parameters (days of therapy, DOTs). Binary data on drug exposure to active control drugs was also replaced with more graded, numeric exposure data in the Amendment 2 analyses.

Another change in Amendment 2 analyses was that a proxy for maternal socioeconomic status was introduced into the propensity score in the logistic regression model. Maternal socioeconomic status was approximated based on the expected socioeconomic status of the micro-region of her residence. Determination of the micro-regional socioeconomic status of towns / villages in Hungary is described in Section 9.8.1.

In addition, county of maternal residence and rural / urban status of maternal residence were also integrated into the propensity score, to reflect geographic effect as a recognized confounder (7, 9, 10).

Amendment 1 results indicated that maternal age was outside of the investigated age categories (i.e. the range of 15-45 years) in about 0.1% of pregnancies. Although these extreme values of maternal age may be biologically plausible, the extensive experience of RxTarget Kft in OEP database analyses suggests that extreme maternal age values reflect most probably incorrect data entry. Accordingly, the amendment 2 analyses of spontaneous abortion risk have excluded all pregnancies with maternal age <15 years or maternal age >45 years.

In summary, Protocol Amendment 2 introduced the following changes in the analysis of spontaneous abortion risk:

- In the regression models of the main analysis and all sensitivity analyses, binary (yes/no) drug exposure variables were replaced by numeric drug exposure variables (filled prescriptions expressed in DOTs). This change is consistently applied for butoconazole as well as for all therapeutic controls and active controls;
- The propensity score also included the socioeconomic status of the maternal residence at micro-region level, and rural/urban status of maternal residence, beyond the previously included variables;
- Pregnancies with maternal age <15 years or maternal age >45 years were excluded from the Amendment 2 analyses.

9.1.2. Design of the congenital anomaly case-control study

The study has not been analysed as planned in the original protocol, as justified in Protocol Amendment 2. In brief, the rationale for this is that the original study protocol lost the medical follow-up of about 440 000 live births, and the exact hierarchy of rules for redundant and conflicting pregnancy outcome codes has not been defined in the original protocol, making pregnancy outcomes ambiguous in cases with multiple conflicting outcome records. All results are provided according to Protocol Amendment 2 and Protocol Amendment 1.

9.1.2.1. Amendment 1 study design and rationale

9.1.2.1.1. Definition of cases and controls

The intention of this study was 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" was 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 consisted of live births without congenital anomaly, similarly to previous studies (19-23). In some sensitivity analyses, the control group was defined as the pooled group of all live births and stillbirths without congenital anomaly / foetal defect (3). All pregnancy outcomes in these analyses were identified as pre-specified in Annex 3.1 of Protocol Amendment 1. Sensitivity analyses pre-planned to test the robustness of the results are summarized in Table 9.G.

Table 9.G. Amendment 1 CA models, main and sensitivity analyses

Planned analyses of teratogenic risk	
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 was applied (as specified in Protocol Amendment 1 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 conversion.
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 Protocol Amendment 1 Annex 3.2.) are excluded.

* In pregnancies with late AFP reports an alternative Day 1 estimate was applied, as specified in Section 9.8.2.

Rationale for these sensitivity analyses: sensitivity analyses 1, 2, 4, and 9 intend 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 (24). 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.

9.1.2.1.2. Time periods of drug exposure

In this analysis, drug exposure was evaluated in the following periods of pregnancy:

- first trimester (19, 25)
- first month (before organogenesis) (25, 26)
- second month (25, 27)
- third month (25, 27)

- second and third month (the critical period for congenital anomalies) (21, 23, 27, 28)
- after the first trimester (21, 23)

9.1.2.1.3. Confounding factors

In most observational epidemiological studies confounding can be an important source of bias. This is also true for studies on the effect of maternal drug use on birth defect risks. Different methods exist for the control of confounding factors. When large datasets are analysed, the most efficient way to control for confounding is to adjust for the confounders in the statistical analysis. The most common way to do this is by using a logistic regression model (18). 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, confounding factors considered are listed in Table 9.H (22, 23).

Table 9.H. Confounding factors considered in HCCSCA studies.

Confounding factors
sex
birth week in birth year
district of parent's residence
maternal age (<20year / 20-29year / >29year)
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 (19, 21, 25) and parity (number of previous live births) (19, 21, 25). In addition, the van Gelder study included a wide range of additional confounders, 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 (25). 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 at the technical definitions in Section 9.1.2.2). 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. The selected confounding factors with their technical definitions are provided in Section 9.1.2.2. 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 (18). The current study adjusted 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 is categorized as „village" or „town" in all of the counties.

The indication treated may also be a confounding factor in the analysis of congenital anomalies, although none of the investigated vaginal candidiasis drugs was associated with increased risk of congenital anomalies in the Rosa study (3). The inclusion of therapeutic controls in our study allows for the evaluation of contrasts across various gynecology anti-infective drugs.

To adjust for the confounder(s) in the statistical analysis, a logistic regression model was applied, as recommended in a recent review on the problem of confounding in studies of the effect of maternal drug use on pregnancy outcome (18). The logistic regression model is a regression method used to study the effect of an exposure of interest on the risk of an outcome conditional on one or more confounding factors in case-control studies. (18).

9.1.2.2. Amendment 1 technical definitions

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

- Exposure to gynecology anti-infectives in the relevant time periods

Gynecology anti-infectives	ATC codes
butoconazole	G01AF15
miconazole (local)	G01AF04, D01AC20
miconazole (systemic)	A01AB09
clotrimazole	G01AF02, D01AC01
metronidazole (local)	G01AF01; D06BX01
metronidazole (systemic)	P01AB01, J01XD01
nystatin (local)	G01AX
nystatin (systematic)	A07AA02

- Exposure to active control drugs in the relevant time periods

Active control drugs	ATC codes
carbamazepine	N03AF01
isotretinoin (local)	D10AD04
isotretinoin (systemic)	D10BA01
lithium	N05AN01
valproic acid	N03AG01

- 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 in the last 4 years before current pregnancy:
        - YES: history of BNO, OENO and HBCS codes specific for live birth (for listing, see Protocol Amendment 1 Annex 3.1.2.) in the last 4 years before index date; and/or any offspring TAJ number recorded in the OEP database belonging to the same mother, in the last 4 years before index date.
        - 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, O3110, Z3510* (3-digit BNO codes represent all 5-digit BNO codes starting with the indicated 3 digits); history of OENO codes specific for spontaneous abortion: *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 filled prescription for drugs belonging to ATC A10.
  - 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

9.1.2.3. Changes introduced by Protocol Amendment 2

Amendment 2 changes in the analysis of teratogenic risk included the modification of the logistic regression model, alterations in the definition of cases and controls, and changes in the planned sensitivity analyses. There was no change in the investigated drugs and in drug exposure windows.

9.1.2.3.1. Changes in the logistic regression model of congenital anomaly risk

Similarly to model changes in the spontaneous abortion risk analyses, the logistic regression model of congenital anomaly risk was modified in the following way:

- Pregnancies with maternal age <15 years or maternal age >45 years have been excluded from the Amendment 2 analyses;
- In the regression models of the main analysis and all sensitivity analyses, binary (yes/no) drug exposure variables have been replaced by numeric drug exposure variables (filled prescriptions expressed in DOTs). This change is consistently applied for butoconazole as well as for all therapeutic controls and active controls;
- The propensity score also included the socioeconomic status of the maternal residence at micro-region level (see in Section 11.8.1), and urban/rural status of maternal residence beyond the currently included variables.

9.1.2.3.2. Definition of cases and controls

In the Amendment 2 analyses of congenital anomalies, 35 alternative definitions were applied to cases and controls. For justification and details, please see Protocol Amendment 2, Annex 3.1.4.

For 33 of the 35 alternative definitions (al1, al2, al10, al15, al17, al34, al101, al40, al49, al52, al58, al61, al97, al21, al22, al55, al59, al66, al67, al81, Q383, Q621, Q623, Q638, Q639, Q649, RG01, RG03, RG10, RG11, RG12, RG13, and RG14; for details, please see Protocol Amendment 2 Annex 3.1.4.), cases were defined as live birth, stillbirth, or elective termination due to foetal defect with reported ICD codes belonging to the appropriate code groups in the relevant time

period (from 8 months before live birth, up to 1 year after live birth; from 6 months before stillbirth, up to 3 months after stillbirth; or in ± 3 months around the date of elective termination).

In these analyses, controls were defined as live births without any congenital anomaly code (as listed in EUROCAT group al1) during pregnancy or until the age of 1 year.

Special considerations apply to two further alternative definitions (al100, and RG04) as detailed below.

Special considerations for the EUROCAT subgroup al100

This EUROCAT subgroup is called "Persistent ductus arteriosus as only congenital heart defect in term infants (gestational age >37 weeks)". This subgroup was analysed with the following modifications:

- Cases were defined as live births,
  - with >37 weeks gestational age, and
  - with a Q250 ICD code in their first year after birth, and
  - without any other congenital heart defect anomaly codes (as listed in EUROCAT group al17) during pregnancy or until the age of 1 year.

- Controls were defined as livebirths with >37 weeks gestational age, without any congenital anomaly codes (as listed in EUROCAT group al1) during pregnancy or until the age of 1 year.

Special considerations for the custom subgroup RG04

The intention of this custom code subgroup analysis was to focus on abdominal wall defects, a recognized nonclinical safety signal for butoconazole in the rat (see Section 7 of the protocol for details). The relevant EUROCAT code subgroup (al49) includes ICD-10 codes Q792, Q793, and Q795, which codes were hardly reported in the OEP database in 2005. The potentially relevant intervention codes OENO 55340, 55350, 55358, 55359, 55360, 55361, 55369 are not included in EUROCAT definitions but are more frequently reported to the OEP database than the ICD codes belonging to al49. Accordingly, beyond the analysis of al49, a custom subgroup of all these codes have also been formed to analyse the risk of abdominal wall defects (marked as RG04). A time-dependent analysis revealed that the interventions associated with abdominal wall defects were typically reported after the first year (see the last column of **Table 3.1.4.3.B** in Annex 3.1.4 of Protocol Amendment 2). For this reason, the case-control analysis applying the RG04 definition of congenital anomalies has been performed with the following modifications:

- Cases and controls were restricted to live births with 3-year follow-up data (i.e. only live births in the 2005-2009 period were included);
- Cases were defined as live births with at least one ICD-10 or intervention code report belonging to RG04 in the first 3 years after birth;
- Controls were defined as all other live births with 3-year follow-up data, without any other congenital anomaly codes (as listed in EUROCAT group al1) during pregnancy or until the age of 3 years.

9.1.2.3.3. Sensitivity analyses

For each alternative definition of cases and controls, 1 main analysis and 8 sensitivity analyses have been applied as detailed in Table 9.I.

Table 9.I. Amendment 2 CA models, main and sensitivity analyses

	Day1 of pregnancy = AFP-107 days*	Day1 = AFP-121 days*	Day1 = AFP-135 days*
all outpatient reports included	Sensitivity analysis 1 (S1)	Main analysis (M)	Sensitivity analysis 2 (S2)
isolated outpatient reports excluded	Sensitivity analysis 3 (S3)	Sensitivity analysis 4 (S4)	Sensitivity analysis 5 (S5)
all outpatient reports excluded	Sensitivity analysis 6 (S6)	Sensitivity analysis 7 (S7)	Sensitivity analysis 8 (S8)

**In pregnancies with late AFP reports, an alternative Day 1 estimate was applied (as specified in Protocol Amendment 2 Annex 3.2.).*

Given that cases / controls are defined in 33+2 alternative ways; 1 main + 8 sensitivity analyses apply to all definitions; 6 exposure windows for 13 drug groups are investigated; 3 levels of model adjustment are applied; and gynecology drug exposure unit was either the days of therapy (DOTs) or the number of treatment cures, all together 35 x 9 x 6 x 13 x 3 x 2 = 147,420 pieces of logistic regression models have been composed on the risk of drug esposure in Amendment 2 analyses (not mentioning models for maternal age group effects).

No formal correction to multiple comparisons have been done in the analyses. Accordingly, any positive finding must be interpreted carefully, considering the number and the strength of positive signals across multiple sensitivity analyses / exposure periods for a certain drug/malformation association. Moreover, to reduce the complexity of our findings, only results of the fully adjusted models are used for study conclusions, and sensitivity analyses with irrealistic number of cases are neglected. For this purpose, malformation rates were calculated as the number of cases divided by 493,535 live births in the study for all sensitivity analyses. For comparison, reported rates at the Hungarian Congenital Anomaly Registry were also calculated as the sum of reported rates with the corresponding individual codes – note that this estimate may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}. Based on these comparisons, irrelevant sensitivity analyses were identified along the following criteria: i) analyses with the closest match to HCAR reporting rates are always relevant; ii) sensitivity analyses with lower reporting rates than the closest match were always relevant (probably reflecting more severe cases); iii) sensitivity analyses with up to 2x the HCAR reporting rates were always relevant (assuming up to 50% under-reporting to the HCAR); and iv) other sensitivity analyses are considered to be not relevant. For details, please see Sub-sections 15.3.1-15.3.35.

9.1.3. Design of Amendment 2 low birthweight analyses

Preliminary descriptive results calculated per Protocol Amendment 1 revealed an apparent increase of low birthweight newborns from butoconazole exposed pregnancies, while clotrimazole exposure was associated with an apparent protective effect against low birthweight. Previously published studies also described a protective effect of clotrimazole against preterm birth (29-31). Note that all of these studies analysed the same 1-2% sample of the Hungarian population.

The descriptive analyses in our study were not controlled for potential confounders. Recognized risk factors for low birthweight include risk factors for intrauterine growth restriction (e.g.

maternal cigarette smoking, alcohol and caffeine consumption, caloric intake during pregnancy, maternal height and pre-pregnancy weight, paternal weight and height, parity, history of prior low birthweight infants, maternal cardiopulmonary or renal medical conditions, infant sex and birth order (32-34)). In developed countries, the far most important factor is cigarette smoking, followed by poor gestational nutrition and low pre-pregnancy weight (32).

Preterm birth also contributes to elevated risk of low birthweight. Recognized risk factors for preterm birth include pre-pregnancy weight, prior history of prematurity or spontaneous abortion, cigarette smoking, uterine myomas, maternal age, maternal Hb concentration, chronic stress, employment status, maternal periodontitis, acute and chronic maternal diseases, inadequacies in prenatal care, genitourinary infections, infant gender, birth order, and district of mother's residence. (30, 32-37).

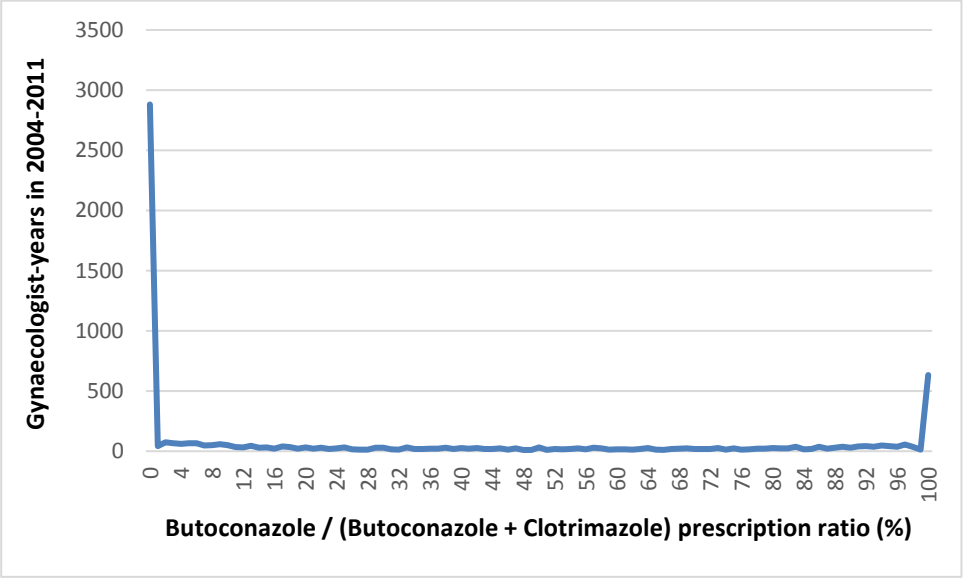
Unfortunately, most of the above potential confounders can not be captured in the OEP database. As an effort to exclude any confounding by unmeasurable risk factors, a quasi-randomized study design was planned for the Amendment 2 birthweight analyses: to exclude the possibility of an association between maternal characteristics and the selection of butoconazole or clotrimazole by their gynaecologists (i.e. confounding by indication), the Amendment 2 birthweight analyses included only unexposed pregnancies, and those pregnancies exposed to butoconazole or clotrimazole prescriptions of doctors with homogenous prescription pattern in the relevant calendar years.

Homogenous prescription pattern of a doctor was defined in the following way:

- the doctor had a valid licence in gynecology, and had prescribed at least 10 doses of (butoconazole + clotrimazole) in total in the relevant calendar year;
- and his/her butoconazole / (butoconazole + clotrimazole) prescription ratio had been 0% or 100% in the relevant calendar year.

The rationale behind this patient population restriction is that different patient characteristics within the doctor's practice could underlie patient-specific drug selection decisions in non-homogenous prescription practices. In contrast, patient chracteristics probably did not shape drug selection in practices where all patients received the same (butoconazole or clotrimazole) drug. Our pilot analyses suggested that a significant fraction of gynaecologist-years with ≥10 annual butoconazole+clotrimazole prescriptions applied a homogenous prescription pattern (**Figure 9. A**).

Figure 9.A. Histogram of gynaecologist-years in 2004-2011 with different butoconazole / (butoconazole + clotrimazole) prescription ratios.



Homogenous prescription patterns are represented by the spikes at 0% and 100%. Only gynaecologist-years with at least 10 (butoconazole + clotrimazole) prescriptions are included.

Potential between-practice differences in patient characteristics were intended to be controlled for by the inclusion of the following socio-economic proxies in the logistic regression models:

- micro-regional development status of the maternal residence (as determined in Section 9.8.1);
- urban / rural status of maternal residence.

The effect of butoconazole and/or clotrimazole exposure on birthweight was to be analysed in the below logistic regression models. All included variables were binary (yes / no) in the regression models, with "no" value as the reference case. Pregnancies with multiple / combined butoconazole and clotrimazole exposures were not excluded (unless any of the butoconazole or clotrimazole prescriptions were written by a doctor with not homogenous prescription pattern in the calendar year of prescription).

Main analysis:

$P_{(\text{birthweight } <2500g)} \sim B_{11}, B_{12}, B_{13+}, C_{11}, C_{12}, C_{13+}, B_{21}, B_{22}, B_{23+}, C_{21}, C_{22}, C_{23+}, B_{31}, B_{32}, B_{33+}, C_{31}, C_{32}, C_{33+}, S_{HH}, S_{LHH}, S_{LHH\text{-}K}, R;$

where B_{1x} and C_{1x} stand for exactly x prescribed butoconazole (B) or clotrimazole (C) therapies in the first trimester; and B_{2x}, C_{2x}, B_{3x} and C_{3x} stand for exactly x prescribed butoconazole (B) or clotrimazole (C) therapies in the second and third trimester, respectively. When x = "3+", three ore more butoconazole and clotrimazole therapies were prescribed in the indicated trimester, respectively. In the birthweight analyses, one filled butoconazole prescription indicates one butoconazole therapy; while one filled prescription of cotrimazole vaginal tablet (3x or 6x) corresponds to 1 or 2 clotrimazole therapies, respectively. S_{HH}, S_{LHH}, and $S_{LHH\text{-}K}$ stand for maternal residence microregional development status characteristics: deprived ("Hátrányos Helyzetű"), most deprived ("LegHátrányosabb Helyzetű"), and most deprived requiring complex interventions ("Komplex programmal segítendő leghátrányosabb helyzetű), respectively (see also Section 9.8.1); and R stands for rural status of maternal residence. All included variables

are binary (yes / no) variables in the regression model, all with "no" value as the reference case;

Sensitivity analyses:

$P_{(\text{birthweight } <2500g)}$ ~ B_{11+}, C_{11+}, S_{HH}, S_{LHH}, S_{LHH-K}, R;

where B_{11+} and C_{11+} stand for at least 1 prescribed butoconazole (B) and clotrimazole (C) therapy in the first trimester, respectively. Note that all included variables are binary (yes / no) in the regression models, with "no" value as the reference case.

$P_{(\text{birthweight } <2500g)}$ ~ B_{11}, B_{12}, B_{13+}, C_{11}, C_{12}, C_{13+}, S_{HH}, S_{LHH}, S_{LHH-K}, R;

$P_{(\text{birthweight } <2500g)}$ ~ B_{D1}, B_{D2}, B_{D3+}, C_{D1}, C_{D2}, C_{D3+}, S_{HH}, S_{LHH}, S_{LHH-K}, R;

where B_{Dx} and C_{Dx} stand for exactly x prescribed butoconazole (B) or clotrimazole (C) therapies during all pregnancy (overall exposition in the 3 trimesters). B_{Dx} and C_{Dx} are binary (yes / no) variables in the regression model, all with "no" value as the reference case;

$P_{(\text{birthweight } <2000g)}$ ~ B_{11}, B_{12}, B_{13+}, C_{11}, C_{12}, C_{13+}, B_{21}, B_{22}, B_{23+}, C_{21}, C_{22}, C_{23+}, B_{31}, B_{32}, B_{33+}, C_{31}, C_{32}, C_{33+}, S_{HH}, S_{LHH}, S_{LHH-K}, R;

$P_{(\text{birthweight } <2000g)}$ ~ B_{11+}, C_{11+}, S_{HH}, S_{LHH}, S_{LHH-K}, R;

$P_{(\text{birthweight } <2000g)}$ ~ B_{11}, B_{12}, B_{13+}, C_{11}, C_{12}, C_{13+}, S_{HH}, S_{LHH}, S_{LHH-K}, R;

$P_{(\text{birthweight } <2000g)}$ ~ B_{D1}, B_{D2}, B_{D3+}, C_{D1}, C_{D2}, C_{D3+}, S_{HH}, S_{LHH}, S_{LHH-K}, R;

Birthweight (grams) ~ B_{11}, B_{12}, B_{13+}, C_{11}, C_{12}, C_{13+}, B_{21}, B_{22}, B_{23+}, C_{21}, C_{22}, C_{23+}, B_{31}, B_{32}, B_{33+}, C_{31}, C_{32}, C_{33+}, S_{HH}, S_{LHH}, S_{LHH-K}, R;

Birthweight (grams) ~ B_{11+}, C_{11+}, S_{HH}, S_{LHH}, S_{LHH-K}, R;

Birthweight (grams) ~ B_{11}, B_{12}, B_{13+}, C_{11}, C_{12}, C_{13+}, S_{HH}, S_{LHH}, S_{LHH-K}, R;

Birthweight (grams) ~ B_{D1}, B_{D2}, B_{D3+}, C_{D1}, C_{D2}, C_{D3+}, S_{HH}, S_{LHH}, S_{LHH-K}, R;

For all of these models, the following adjustments were planned:

- crude odds ratios from univariate analyses are presented for all included model factors;

- adjusted(1) odds ratios are adjusted for all other drugs (in case of drugs) or for all other socio-economic status indicators (in case of a socioeconomic indicator model);

- adjusted(2) odds ratios are adjusted for all variables in the model.

To qualitatively check the assumed comparability of butoconazole and clotrimazole exposed pregnancies in the above analyses, descriptive statistics are provided on selected measurable patient characteristics in Section 10.2.6 for patient groups of different socioeconomic status and drug exposure.

9.2. Setting

9.2.1. Persons and place

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

9.2.2. 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 were also evaluated in the previous 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.

9.3. Subjects

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. Live births where the mother's and the child's TAJ number could not be paired to each other in the database have been excluded from the study.

In Amendment 2 models on low birthweight, pregnancies exposed to butoconazole or clotrimazole prescriptions of gynaecologists with inhomogeneous prescription patterns were excluded to allow a quasi-randomization approach (for details, please see Section 9.1.3).

9.4. Variables

9.4.1. Pregnancy outcomes

According to the relevant guideline (1), 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 of the Protocol. It was expected that the provided technical definitions cover the vast majority of pregnancies in the relevant time period (an exception is mola hydatiosa which was not investigated in this study, in line with the CHMP guideline (1).

Birth weight data in the OEP database have also been analysed. For more details, please see Protocol Amendment 2 Section 9.7.11.

9.4.2. Time periods of the pregnancy

According to the relevant guideline (1), 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. Risk of low birthweight will be evaluated for first trimester, second trimester, third trimester, and during pregnancy drug exposures. For more details and justifications, please see Section 9.7 and Protocol Amendment 1 Annex 3.2.

9.4.3. Investigated drugs

- butoconazole (test drug)
- clotrimazole, miconazole, nystatin, metronidazole (therapeutic controls)
- diclofenac, naproxen, celecoxib, ibuprofen, rofecoxib, indomethacin (confounding factors and active controls in the spontaneous abortion case-control study);
- isotretinoin, carbamazepine, lithium, valproic acid (confounding factors and active controls in the teratogenicity case-control study).

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.

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

Some of the active control drugs are also available both in locally administered and systemic formulations (diclofenac, naproxen, ibuprofen, indomethacin, isotretinoin), which were also analysed separately.

9.4.4. 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 (18), 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 include a larger 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.

9.4.5. Drug exposure

According to the Original Protocol and Protocol Amendment 1, drug exposure was analysed as a binary parameter (yes/no) based on the evidence of at least one filled prescription in the OEP database in the relevant time periods.

In contrast, the analyses of Protocol Amendment 2 consider drug exposure as a quantitative parameter (filled prescriptions calculated in DOTs, i.e. days of therapy as declared for all medicinal products in Hungary in the PUPHA (Public Database of Reimbursable Medicines in Hungary) list by the OEP). However, it has been realized during data analysis that the recommended length of therapy is variable across and within acive ingredients (e.g. butoconazole is administered for 1 day, while clotrimazole is administered for 3 or 6 days, depending on the selected intravaginal formulation). Accordingly, it would not be clinically meaningful to compare the risk of one day of butoconazole therapy to one day of clotrimazole therapy. Instead, the risk linked to one completed cure is the clinically relevant parameter to be compared across the therapeutic alternatives. For this reason, the approved Summary of Product Characteristics of all gynecology anti-infectives have been searched for recommendations on treatment duration, and these pieces of information, together with data on the drug content per package, were used to calculate the ratio of completed cures per package for all gynecology anti-infective products. The calculated ratios showed that for all of the included gynecology anti-infective products, the number of prescribed packages was equal to the number of completed cures (except for a metronidazole solution for infusion, where the prescription of any number of infusion bottles within 7 calendar days were considered to be part of a single cure).

For active controls, drug exposure has not been expressed in number of cures, due to the high number of the relevant products and also due to their less specific treatment duration. Accordingly, exposure to active controls is expressed in DOTs in all Amendment 2 analyses.

9.5. Data sources and measurements

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 et al., 2009a; Acs et al., 2009b; Acs et al., 2010; Banhidy et al., 2007; Banhidy et al., 2011a; Banhidy et al., 2011b; Banhidy et al., 2011c; Czeizel et al., 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, 2013a)).

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 were considered to be 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 repeated service use in a sufficiently long period are also considered to be a valid indicator of the disease. 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 Section 9.8.2).

9.6. Bias

See at study limitations in Section 11.2.

9.7. Study size

According to national statistics provided by Hungarian Central Statistical Office, numbers of pregnancy outcomes occurring in the relevant time period are shown in Table 9.J.

Table 9.J. Expected study size based on KSH data on pregnancy outcomes in the investigated 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 KSH (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 was expected that most of these cases were included in the OEP database. Accordingly, the size of the current study was planned to be similar to a recently published population-based analysis in Denmark (1 221 546 pregnancy

outcomes, (5)) and about one order of magnitude larger than the largest published study on other gynecology anti-infectives before (104 339 pregnancies, (3). The single published human study on butoconazole investigated 229 101 completed pregnancies and found no increased risk in women with first-trimester butoconazole exposure (38).

No formal sample size calculation was performed for this study. To maximize the power and to avoid selection bias, all pregnancies in the relevant time period were intended to be included (where the mother-children TAJ number pairs could be established in the database). The expected size of the study was considered to be adequate, i.e. similar or larger than previous published studies on adverse drug effects on pregnancy.

In the congenital anomaly case-control study, code groups to be analysed in Amendment 2 were determined based on the expected power of the planned analyses. For details, please see Protocol Amendment 2 Annex 3.1.4. Based on the observed patient numbers and exposure data applying the selected 35 alternative definitions of congenital anomalies, exact statistical power calculations have been conducted using the Whitemore (1981) and Hsieh (1989) approach discussed in {Hosmer Jr, 2004 #64} (Section 8.5, equations 8.45 – 8.47 on page 363). Calculated powers and the necessary input data are included in the Tabular summary of Amendment 2 results on congenital anomaly risks (see at Section 5.1).

9.8. Data transformation

9.8.1. Estimation of maternal socioeconomic status

Micro-regions of Hungary were systematically characterised and ranked by a complex indicator of socioeconomic status in 2007, based on 31 parameters in 5 major groups (economic, infrastructural, societal, social, and employment characteristics)(39, 40). Based on this ranking, 94 of the 174 micro-regions were identified as deprived, of which 47 were classified as “most deprived” and among those, 33 were classified as “most deprived, needing complex intervention”.

In 2011, the number of micro-regions increased to 175 when the “Ajkai” micro-region was divided to the “Devecseri” and “Ajkai” micro-regions after an industrial disaster (spill at the alumina plant Magyar Alumínium Zrt. (MAL Zrt.) Ajkai Timfoldgyar, destroying or damaging ~300 houses). The new, “Devecseri” micro-region covered the damaged area and has been classified as “most deprived, needing complex intervention” from 2011.

In the OEP database, postal code is available for the residence of all patients. Maternal residence postal codes were linked to village / town names by the postal code database of Magyar Posta (downloaded from http://www.posta.hu/ugyfelszolgalat/iranyitoszam_kereso, version 19 June 2015).

Village/town names were linked to micro-regions as listed in Appendix 1 of Act XXI of 1996, and Act CXLIX of 2010 (the latter established the newly formed “Devecseri”micro-region). Socioeconomic status of micro-regions was determined as listed in the 311/2007(17th November) Decree of the Hungarian Government. For the time period 2011-2012, the socioeconomic status of the newly formed “Devecseri” micro-region was set to “most deprived, needing complex interventions”, along the 116/2011 (7th July) Decree of the Hungarian Government. This isolated minor change could have marginal relevance in the present study, therefore the socioeconomic status of the micro-regions have been determined based on the 311/2007(17th November) Decree of the Hungarian Government.

Micro-regional socioeconomic status of maternal residence is categorized as NH (Nem hátrányos helyzetű / not deprived), HH (hátrányos helyzetű / deprived), LHH (leghátrányosabb helyzetű / most deprived), and LHH-K (leghátrányosabb helyzetű, complex beavatkozást igénylő / most

deprived requiring complex intervention). The corresponding binary variables (dummies) handle these categories as mutually exclusive ones:

Binary variables	Micro-region categories			
	NH	HH	LHH	LHH-K
S_{HH}	no	yes	no	no
S_{LHH}	no	no	yes	no
S_{LHH-K}	no	no	no	yes

S_{HH}, S_{LHH}, and S_{LHH-K} were introduced into the regression models by the following ways:

- Spontaneous abortion models: S_{HH}, S_{LHH}, and S_{LHH-K} included in the propensity score in the adjusted(2) models;
- Congenital anomaly models: S_{HH}, S_{LHH}, and S_{LHH-K} included in the propensity score in the adjusted(2) models;
- Birthweight analyses: S_{HH}, S_{LHH}, and S_{LHH-K} directly included in the regression models as indicated in Section 9.1.3.

9.8.2. Determination of gestational age in the OEP database

9.8.2.1. Calculation of Day 1 of pregnancy

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 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 are overwritten with an ***alternative estimate*** as follows.

9.8.2.2. Criteria of „late AFP reporting"

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

9.8.2.3. 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, all of the following condition and intervention codes are considered to be "pregnancy-specific":

- all HBCS, BNO and OENO codes listed in Protocol Amendment 1 Annex 3.1.1. and Annex 3.1.2.
- pregnancy-related BNO and OENO codes not specific to pregnancy outcome (see Table 9.K).

Table 9.K. Pregnancy-related BNO and OENO codes not specific to pregnancy outcome

BNO	Description (in Hungarian)
N9400	Középidős fájdalom (Mittelschmerz)
O....	any BNO code starting with „O" and not listed as outcome-specific codes in Protocol Amendment 1 Annex 3.1.2.
P9630	Az újszülött tág koponyavarratai
P9640	A terhesség befejeződése, magzat és újszülött
P9650	Méhen belüli beavatkozások szövődményei, m.n.o.
P9680	A perinatális időszakban keletkező egyéb meghatározott állapotok
P9690	A perinatális időszakban keletkező állapot, k.m.n.
S3762	Terhes méh sérülése
S3767	Placenta sérülése
Z3210	Terhesség, bizonyított
Z33H0	Véletlen észlelt terhes állapot
Z3400	Terhesgondozás első terhesség esetén
Z3410	Egyéb egészségügyi ellátás terhes személynél
Z3480	Terhesgondozás egyéb normális terhességben
Z3490	Terhesgondozás, k.m.n.
Z3500	Terhesgondozás korábbi terméketlenséget követően
Z3510	Terhesgondozás korábbi vetélést követően
Z3520	Terhesség problematikus és terhelő szülészeti előzményt követően
Z3540	Terhesgondozás sokat szült nőnél
Z3550	Terhesgondozás idős (késői) elsőszülőnél
Z3560	Terhesgondozás igen fiatal elsőszülőnél
Z3570	Terhesgondozás szociálisan veszélyeztetett terhesnél
Z3580	Terhesgondozás egyéb veszélyeztetett terhesnél
Z3590	Terhesgondozás k.m.n. veszélyeztetett terhesség esetében
Z3600	Chromosoma rendellenesség szűrése születés előtt
Z3610	Szülés előtti AFP szűrés

Z3620	Születés előtti szűrés magzatvízből
Z3630	Születés előtti UH és egyéb fiz. módszerű szűrés fejl. rendell. iránt
Z3640	Magzati növekedési elmaradás eszközös, ultrahangos szűrése
Z3650	Magzati isoimmunisatio szűrése születés előtt
Z3680	Születés előtti szűrés, egyéb
Z3690	Születés előtti szűrővizsgálat, k.m.n.
Z3900	Szülés utáni ellátás és vizsgálat
OENO	**Description (in Hungarian)**
14780	Chorion biopsia
14781	Chorion biopsia, transvaginalis, UH vezérelt
14782	Chorion biopsia, transabdominalis, UH vezérelt
36140	Terhességi transabdominalis UH vizsgálat
36141	Terhességi transvaginalis UH vizsgálat
44811	Pathológiás terhes folyamatos kórházi gondozása
46010	Első trimesteri terhesgondozói vizit
46020	Második trimesteri terhesgondozói vizit
46030	Harmadik trimesteri terhesgondozói vizit
57200	Kimeneti fogó műtét, episiotomia nélkül
57210	Kimeneti fogó műtét, episiotomiaval
57220	Üregi fogó műtét
57240	Magzati fej forgatása, fogóval
57250	Medencevégű magzat extractioja
57251	Extendalt lábak kifejtése
57252	Felcsapott karok kifejtése
57254	Fej kifejtése
57255	Belső lábrafordítás és extractio
57256	Külső fordítás, extractio nélkül
57260	Fogó alkalmazása a hátul jövő fejre
57270	Egyszerű fartartásos szülés vezetése
57271	Kettőzött fartartásos szülés vezetése
57280	Fej vacuum-extractio
57300	Burokrepesztés
57320	Belső fordítás és extractio
57380	Episiotomia és ellátása
57530	Amniocentesis
57540	Intrauterin transfusio
57551	Magzati vérvétel
57560	Lepényleválasztás
57561	Lepény retentio manuális kiürítése
57580	Resutura dehiscentiae episiotomiae
57581	Gátsérülés ellátása - szülés után
57582	Másodlagosan gyógyuló episiotomia ellátása
57591	Méhűri betapintás szülés után (Bumm kanál)
57593	Uterus űr tamponálása (szülészeti)
82510	Külső fordítás hosszfekvésbe, harántfekvésű magzat
82511	Külső fejrefordítás, medencevégű magzat
82520	Retroflectált terhes uterus kiemelése
82530	Tartási v. forgási rendellenesség korrekció

89610	CTG szülés alatt
89611	CTG terhesség alatt (NST)
89612	CTG terheléses
91318	Diabeteses gravidák, illetve a gestatios diabetesesek időszakos ellenőrzése
92250	Immunglobulin pótlás (1 egység = 20 ml) újszülöttek ellátása esetén
92501	Szülésindítás intraut. gyógyszer adagolással
92510	Szülésindítás iv. gyógyszer adagolással
92530	Szülésindítás im. gyógyszer adagolással
92540	Szülésindítás burokrepesztéssel
92600	Szülés levezetése
92604	Praeeclampsias terhes szülés vezetése, észlelése
94750	Terhesség alatti torna

Note that many of the above conditions / interventions occur in late-stage pregnancy or around childbirth. However, assuming a maximum 60 days delay of late AFP sampling reports in the OEP database, the calculation formula of the alternative Day 1 estimate relies only on those BNO/OENO/HBCS pregnancy codes which have been reported in the first trimester.

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" were excluded from a sensitivity analysis of congenital anomaly risk (sensitivity analysis 9 in Amendment 1 analyses). As an additional measure against the remaining uncertainty, two further sensitivity analyses are included in Protocol Amendment 1 with alternative definitions of Day 1 of pregnancy:

analysis ID	First day of pregnancy
main analysis	{AFP reported date} minus 121 days
CA_sensitivity analysis_1	{AFP reported date} minus (121+14) days
CA_sensitivity_2	{AFP reported date} minus (121-14) days

9.8.2.4. 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).

9.8.2.5. 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).

9.8.2.6. 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.

9.8.3. Cure numbers as exposition units for gynecology anti-infective drugs

Exposure in DOTs were determined as declared for all medicinal products in Hungary in the PUPHA list by the OEP. Exposure in cure numbers was determined based on recommended treatment duration, daily dose, and package size for the particular products as specified in the relevant Summary of Product Characteristics. Accordingly, the number of treatment cures was found to be one for each prescribed package of the investigated gynecology anti-infective drugs, except for a systemic metronidazole product of 1x100ml solution in a bottle containing 500 mg metronidazole. For this product, any number of bottles within 7 days were considered to belong to the same treatment cure. Products with contraindication for gynecology infections (Candibene-ratiofarm 1% spray; Canesten solutions; and metronidazole gels approved for rosacea, not for mucosal application) were excluded both from Amendment 1 and Amendment 2 analyses.

9.9. Statistical methods

9.9.1. Main summary measures

Counts, percentages, means, and standard deviations were calculated as indicated on the corresponding figures / tables in Sections 10.1 – 10.3.

9.9.2. Main statistical methods

In logistic regression models, odds ratios with 95% confidence intervals were estimated (both as crude and adjusted values). For adjustment factors, please see the sections on study design (Section 9.1). In linear regression models on birthweight as a continuous variable, the regression coefficients with their 95% confidence intervals were calculated, adjusted to pre-defined potential confounders as shown in Section 15.4. For statistical tests of low birthweight data in Amendment 1 analyses, Fischer's and Chi-square tests were applied as shown in Section 10.2.5.

9.9.3. Missing values

Pregnancies where maternal and offspring permanent social security IDs could not be matched were excluded from all analyses. Pregnancies with unknown pregnancy outcomes were also excluded from all analyses, except for sensitivity analysis 6 of the spontaneous abortion case-control study where all pregnancies with missing outcomes were assumed to be spontaneous abortions.

In live birth and stillbirth without an AFP screening test in the relevant time period, gestational age at outcome was assumed to be the average gestational age of cases belonging to the same pregnancy outcome with reported AFP screening test dates. In elective termination due to foetal defects without a reported AFP screening test in the relevant time period, the gestational age at elective termination was 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. Foetal defect / congenital abnormality cases and healthy controls without reported AFP screening test in the last 26 weeks before pregnancy outcome were excluded from a sensitivity analysis (CA_sensitivity_4) of the Amendment 1 teratogenicity case-control study.

9.9.4. Sensitivity analyses

Sensitivity analyses in the sponatenous abortion, congenital anomaly, and low birthweight models are detailed in Section 9.1.1.2, Section 9.1.2.3.3, and Section 9.1.3, respectively.

9.9.5. Amendments to the statistical plan

Protocol Amendment 2 analyses were planned to capture all investigated drug exposure on a continuous scale, in the units of „days of therapy" (DOTs). However, comparison of risks associated with a treatment cure is more meaningful clinically than comparison of risks associated with one treatment day. Note that butoconazole requires a single administration while clotrimazole treatment takes 3 or 6 days, depending on the selected product. To compare the congenital anomaly risks associated with one treatment cure, separate models were developed as post-hoc statistical analyses. For the determination of treatment cure numbers, please see section 9.8.3. Note that birthweight effects were pre-planned to be conducted by treatment cure numbers, as specified in Protocol Amendment 2.

9.10. Quality control

The study protocol and both amendments have been 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 has been registered in the EU PAS (ENCEPP) register before the start of data collection (registration number: EUPAS4282).

Quality control of data management at OEP, i.e. at the site of data analysis have been ensured by the qualified personnel and the regulated workflows at OEP. Data output tables received from OEP are presented in the report or attached as separate files (see Section 15.1).

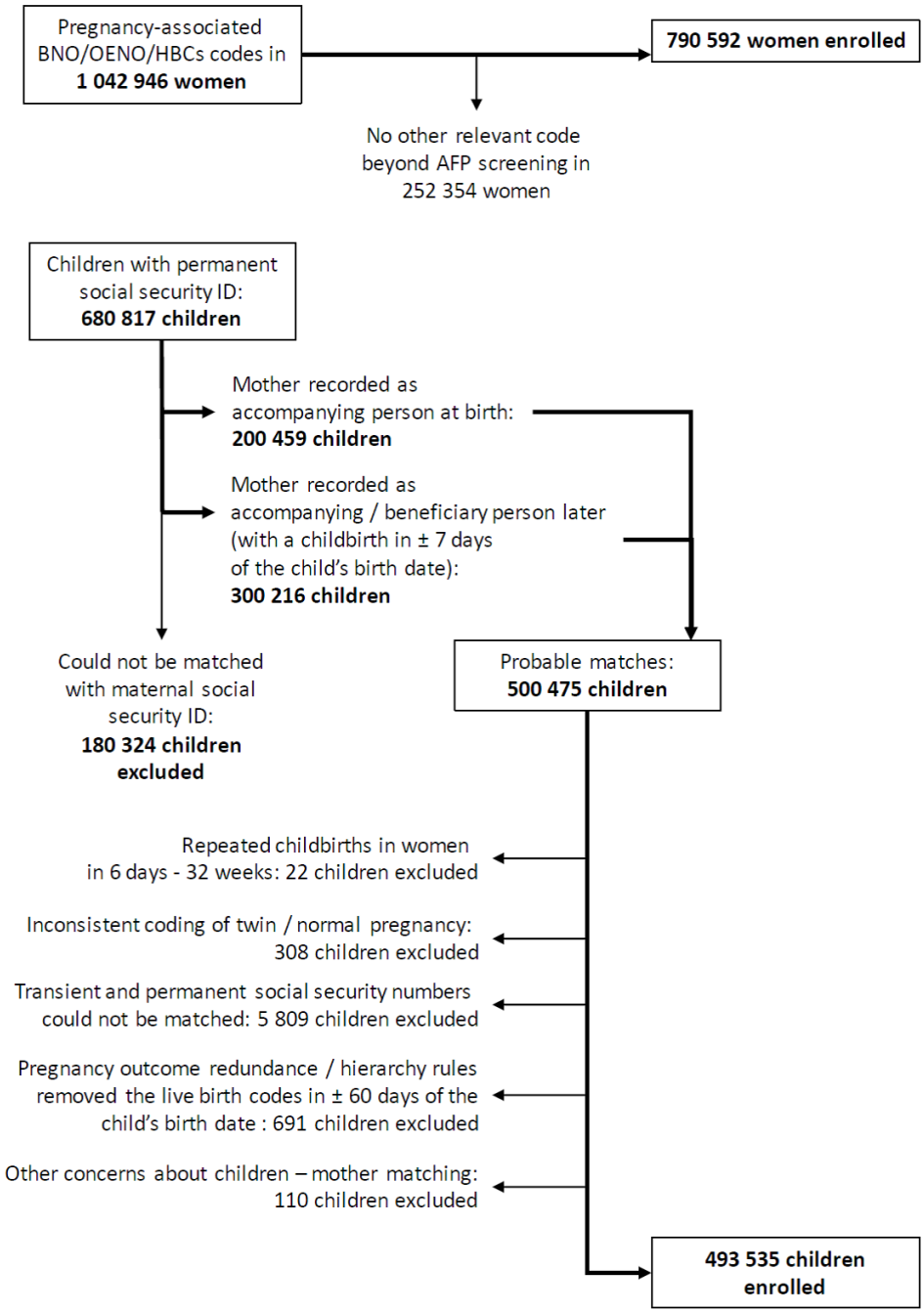
10. Results

All study analyses have been conducted in two ways: according to Protocol Amendment 2 (main analysis); and according to Protocol Amendment 1 (ancillary analysis).

10.1. Participants

The study population is the same in the Amendment 2 and Amendment 1 analyses. Flowchart of mother and offspring enrollment is shown in Figure 10.A. In total, the analyses cover 790,592 women with 1,098,789 identified pregnancies, including 493 535 live births.

Figure 10.A. Women and children enrollment flowchart



10.2. Descriptive data

This was the first study with the intention to determine pregnancy outcomes, pregnancy periods, drug exposure, pregnancy risks and confounding factors solely from the OEP database. In this pioneering exercise, the original study protocol failed to identify most mother – offspring pairs, since it did not match the transient and permanent social security numbers of the investigated children, resulting in the loss of medical follow-up of about 440 000 live births. Moreover, the exact hierarchy of rules for redundant and conflicting pregnancy outcome codes has not been defined in the original protocol, making pregnancy outcomes ambiguous in cases with multiple outcome records. Accordingly, as justified in Protocol Amendment 2, the study has not been analysed as planned in the original protocol. Instead, all descriptive statistics are provided according to Protocol Amendment 2 and Protocol Amendment 1.

10.2.1. Study population characteristics

The study investigated 1,098,789 pregnancies in 790,592 women in the relevant time period. Pregnancy outcomes according to the main and ancillary analyses are shown in **Table 10.A**. Maternal age distributions are shown on **Figure 10.B** for live births and spontaneous abortions.

Table 10.A. Pregnancy outcomes in Amendment 1 and 2 analyses

Outcome	No. of pregnancies	
	main analyses (Amendment 2)	ancillary analyses (Amendment 1)
Ectopic pregnancy	10,554	10,554
Spontaneous abortion	128,156	128,104
Elective termination (no foetal defects or unknown)	301,093	300,958
Elective termination (foetal defects)	0	187
Stillbirth without foetal defects	3376	3,338
Stillbirth with foetal defects	0	38
Live birth without congenital anomaly	342,260	301,407
Live birth with congenital anomaly	151,275	192,128
Unidentified / unknown outcome	162,075	162,075

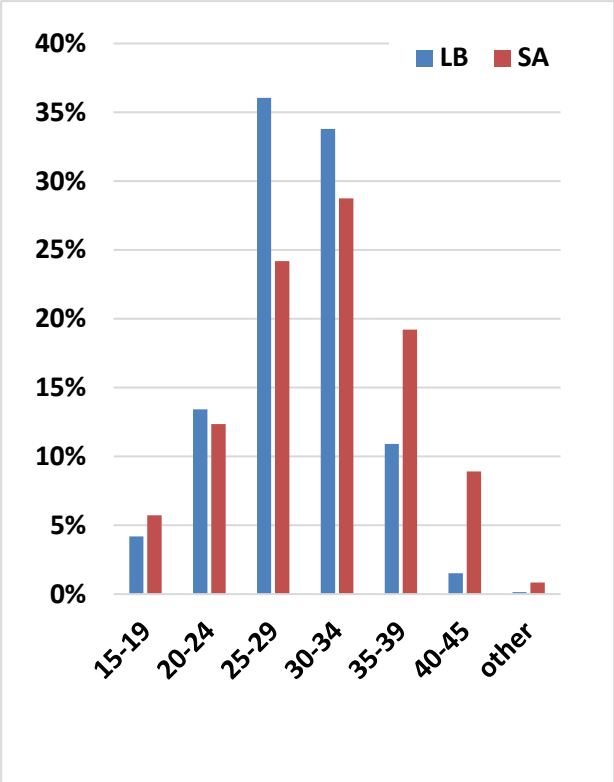


Figure 10.B. Maternal age histogram for spontaneous abortions and live births (Amendment 1).

LB, live births; SA, spontaneous abortions.

To determine the first day of pregnancy, a relevant AFP screening date was found in 4.2% of spontaneous abortions and in 89.5% of live births with at least 180-day long OEP history. The calculated pregnancy durations along the alternative assumptions on the typical day of AFP screening are shown in **Table 10.B**. The Day 121 estimate of typical day for AFP screening records was the most consistent estimate when compared with the typical 40-week ± 2 weeks duration of pregnancy.

Table 10.B. Calculated pregnancy duration by alternative assumptions on the timing of AFP screening

Analysis	Assumption on pregnancy day of AFP screening	Calculated mean pregnancy duration	Calculated SD of pregnancy duration
Control group in the congenital anomaly analyses	Day 107	264.8 days	13.3 days
	Day 121	278.8 days	
	Day 135	292.8 days	
Control group in the al100 congenital anomaly analysis	Day 107	267.0 days	9.5 days
	Day 121	281.0 days	
	Day 135	295.0 days	
Control group in the RG04 congenital anomaly analysis	Day 107	264.7 days	13.37 days
	Day 121	278.7 days	
	Day 135	292.7 days	

10.2.2. Geographic pattern of congenital anomaly diagnoses

Descriptive statistics along the Amendment 1 pregnancy outcome definitions are provided in **Table 10.C** by counties and by urban / rural classification of maternal residences according to their postcodes, including live births without congenital anomaly, live births with congenital anomaly, stillbirth with foetal defects, and elective termination due to foetal defects (altogether 493,760 pregnancies).

Table 10.C. Geographic pattern of congenital anomaly cases in Hungary

Region	Foetal defect / congenital anomaly							
	NO				YES			
	Urban	Rural	n.a.	Total	Urban	Rural	n.a.	Total
Budapest	51,142			51,142	30,886			30,886
Counties								
Bács-Kiskun	10,582	4,130		14,712	7,773	3,157		10,930
Baranya	3,262	1,635		4,897	8,927	3,796		12,723
Békés	7,154	2,268		9,422	3,450	1,086		4,536
Borsod-Abaúj-Zemplén	7,718	4,907		12,625	8,659	5,733		14,392
Csongrád	9,496	3,124		12,620	8,088	2,207		10,295
Fejér	10,079	7,684		17,763	3,422	2,760		6,182
Győr-Moson-Sopron	9,245	6,458		15,703	5,394	3,894		9,288
Hajdú-Bihar	14,219	3,631		17,850	8,121	1,801		9,922
Heves	5,233	6,268		11,501	1,987	2,018		4,005
Jász-Nagykun-Szolnok	9,171	4,135		13,306	2,373	1,179		3,552
Komárom-Esztergom	5,345	2,645		7,990	5,330	2,536		7,866
Nógrád	2,886	3,906		6,792	1,129	1,557		2,686
Pest	31,737	17,782		49,519	15,950	8,061		24,011
Somogy	5,343	4,542		9,885	2,133	1,949		4,082

Region	Foetal defect / congenital anomaly							
	NO				YES			
	Urban	Rural	n.a.	Total	Urban	Rural	n.a.	Total
Szabolcs-Szatmár-Bereg	9,199	7,589		16,788	5,494	5,156		10,650
Tolna	2,255	1,680		3,935	3,458	2,514		5,972
Vas	5,499	3,400		8,899	2,099	1,519		3,618
Veszprém	3,826	2,894		6,720	6,776	4,069		10,845
Zala	4,706	3,325		8,031	3,075	2,116		5,191
Unknown			1,307	1,307			721	721
TOTAL	208,097	92,003	1,307	301,407	134,524	57,108	721	192,353

10.2.3. Time profile of first congenital anomaly diagnoses

The time profile of reporting congenital anomalies after birth has been investigated in a cohort of pregnancies with a live birth outcome in 2005. The intention of this analysis was to explore the proportion of cases with late diagnoses (beyond the age of 1 year), and to overview the relevant BNO and OENO codes corresponding to late diagnoses. For this reason, only BNO and OENO codes reported in the life year of first congenital anomaly diagnosis were investigated. **Table 10.D** and **Table 10.E** summarize the temporal pattern of first congenital anomaly diagnoses together with the corresponding BNO and OENO codes in the Amendment 2 and Amendment 1 analyses, respectively.

Table 10.D. Temporal pattern of CA codes in cases born in 2005 (Amendment 2).
The total number of evaluable live births was 77,026 in 2005. Only those anomalies reported in the life year of first congenital anomaly report are included.

Time periods	No. of children with first report	Relevant BNO / OENO codes in children with first report in this time period
Up to 365 days after pregnancy outcome	24,960	**BNO:** Q6580 (N= 11924); Q6590 (N= 4090); Q2110 (N= 2104); Q6500 (N= 1647); Q0480 (N= 1483); Q6390 (N= 1407); Q3830 (N= 847); Q2100 (N= 792); Q2500 (N= 709); Q6230 (N= 705); Q6490 (N= 680); Q6510 (N= 415); Q6380 (N= 380); Q6520 (N= 321); Q2490 (N= 320); Q8280 (N= 277); Q6210 (N= 243); Q6200 (N= 239); Q6600 (N= 238); Q0460 (N= 214); Q2210 (N= 185); Q5400 (N= 176); Q5490 (N= 165); Q3230 (N= 161); Q5410 (N= 135); Q0490 (N= 131); Q0390 (N= 104); Q8970 (N= 96); Q5520 (N= 96); Q2560 (N= 93); Q2120 (N= 85); Q6880 (N= 81); Q7500 (N= 81); Q6000 (N= 80); Q6480 (N= 79); Q7750 (N= 76); Q7420 (N= 75); Q3210 (N= 67); Q6280 (N= 67); Q6610 (N= 65); Q02H0 (N= 64); Q2480 (N= 62); Q8290 (N= 59); Q6990 (N= 56); P3710 (N= 55); Q8420 (N= 53); Q2090 (N= 53); Q6900 (N= 50); Q3560 (N= 49); Q2510 (N= 48); Q7590 (N= 47); Q3690 (N= 46); Q7020 (N= 44); Q8980 (N= 44); Q6190 (N= 41); Q7000 (N= 40); Q2300 (N= 40); Q2130 (N= 39); Q2230 (N= 38); Q2790 (N= 37); Q7090 (N= 36); Q1200 (N= 36); Q3750 (N= 36); Q4390 (N= 35); Q0400 (N= 34); Q1060 (N= 34); Q4310 (N= 30); Q2280 (N= 30); Q8220 (N= 29); Q6250 (N= 29); Q6320 (N= 28); Q2310 (N= 28);

Time periods	No. of children with first report	Relevant BNO / OENO codes in children with first report in this time period
		Q5480 (N= 27); Q0300 (N= 27); Q3790 (N= 27); Q6310 (N= 27); Q6140 (N= 26); Q3240 (N= 26); Q7490 (N= 26); Q1880 (N= 26); Q6300 (N= 25); Q3360 (N= 25); Q7130 (N= 25); Q3000 (N= 24); Q4380 (N= 24); Q4470 (N= 23); Q3800 (N= 23); Q2880 (N= 23); Q6020 (N= 22); Q6050 (N= 21); Q6130 (N= 21); Q6030 (N= 21); Q3860 (N= 21); Q7950 (N= 21); Q5010 (N= 21); Q3180 (N= 20); Q2190 (N= 20); Q2030 (N= 19); Q3910 (N= 19); Q1320 (N= 19); Q4210 (N= 19); Q7030 (N= 18); Q0590 (N= 18); Q2200 (N= 18); Q5560 (N= 18); Q4200 (N= 18); Q1690 (N= 18); Q6180 (N= 17); Q6810 (N= 17); Q6110 (N= 17); Q2540 (N= 17); Q2330 (N= 17); Q3540 (N= 17); Q4100 (N= 17); Q1780 (N= 17); Q4220 (N= 17); Q8310 (N= 16); Q1000 (N= 16); Q3600 (N= 16); Q3710 (N= 16); Q3780 (N= 16); Q1580 (N= 16); Q8480 (N= 16); Q7010 (N= 15); Q7900 (N= 15); Q5500 (N= 15); Q3900 (N= 15); Q3700 (N= 15); Q3740 (N= 15); Q1300 (N= 14); Q6220 (N= 14); Q3120 (N= 14); D1810 (N= 14); Q2570 (N= 14); Q7480 (N= 14); Q4230 (N= 14); Q7040 (N= 13); Q7510 (N= 13); Q3590 (N= 13); Q3880 (N= 13); Q7180 (N= 13); Q3850 (N= 13); Q8490 (N= 13); Q2580 (N= 13); Q2890 (N= 13); Q2080 (N= 13); Q6400 (N= 12); Q8500 (N= 12); Q3380 (N= 12); Q7580 (N= 12); Q8700 (N= 12); Q2400 (N= 11); Q4420 (N= 11); Q6910 (N= 11); Q2050 (N= 11); Q2430 (N= 11); Q3190 (N= 11); Q7280 (N= 11); Q2220 (N= 11); Q5290 (N= 11); Q7980 (N= 11); Q6920 (N= 10); Q3300 (N= 10); Q2340 (N= 10); Q8380 (N= 10); Q1500 (N= 10); Q3980 (N= 10); Q2180 (N= 10); Q0570 (N= 10); Q3550 (N= 10); Q0680 (N= 10); Q4180 (N= 10). **OENO:** -
In the 2nd year after pregnancy outcome	763 (cumulative: 25,723)	**BNO:** Q2110 Pitvari sövényhiány (N= 81); Q6580 A csípő egyéb veleszületett deformitásai (N= 68); Q3830 A nyelv egyéb veleszületett rendellenességei (N= 46); Q5520 A here és herezacskó egyéb veleszületett rendellenességei (N= 42); Q6490 A húgyrendszer rendellenessége, k.m.n. (N= 41); Q6390 A vese veleszületett rendellenessége, k.m.n. (N= 38); Q6590 A csípő veleszületett deformitása, k.m.n. (N= 29); Q3230 Veleszületett hörgőszűkület (N= 27); Q5560 A hímvessző egyéb veleszületett rendellenességei (N= 20); Q6500 A csípő veleszületett egyoldali dislocatiója (N= 16); Q8220 Mastocytosis (N= 15); Q2100 Kamrai sövényhiány (N= 14); Q6380 A vese egyéb meghatározott veleszületett rendellenességei (N= 14); Q5410 Hypospadiasis a penisen (N= 13); Q6600 Dongaláb (pes equinovarus) (N= 13); Q6230 A vesemedence és húgyvezeték egyéb, elzáródással járó rendellenességei (N= 12); Q7410 A térd veleszületett rendellenessége (N= 11); Q3240 A hörgő egyéb veleszületett rendellenességei (N= 11); Q3210 A légcső egyéb veleszületett rendellenességei (N= 11); Q2500 Nyitott ductus

Time periods	No. of children with first report	Relevant BNO / OENO codes in children with first report in this time period
		arteriosus (N= 10); **OENO:** 55340 Hernioplastica umbilicalis (N= 25); 55350 Reconstructio parietis abdominis (N= 13).
In the 3rd year after pregnancy outcome	421 (cumulative: 26,144)	**BNO:** Q2110 Pitvari sövényhiány (N= 38); Q6390 A vese veleszületett rendellenessége, k.m.n. (N= 25); Q6580 A csípő egyéb veleszületett deformitásai (N= 24); Q6490 A húgyrendszer rendellenessége, k.m.n. (N= 21); Q3830 A nyelv egyéb veleszületett rendellenességei (N= 18); Q5520 A here és herezacskó egyéb veleszületett rendellenességei (N= 16); Q5560 A hímvessző egyéb veleszületett rendellenességei (N= 12); Q3230 Veleszületett hörgőszűkület (N= 11); **OENO:** 55350 Reconstructio parietis abdominis (N= 34); 55340 Hernioplastica umbilicalis (N= 31).
In the 4th year after pregnancy outcome	392 (cumulative: 26,536)	**BNO:** Q2110 Pitvari sövényhiány (N= 46); Q3830 A nyelv egyéb veleszületett rendellenességei (N= 29); Q5560 A hímvessző egyéb veleszületett rendellenességei (N= 26); Q6490 A húgyrendszer rendellenessége, k.m.n. (N= 15); Q6390 A vese veleszületett rendellenessége, k.m.n. (N= 13); Q5520 A here és herezacskó egyéb veleszületett rendellenességei (N= 11); **OENO:** 55350 Reconstructio parietis abdominis (N= 58); 55340 Hernioplastica umbilicalis (N= 47).
In the 5th year after pregnancy outcome	310 (cumulative: 26,846)	**BNO:** Q2110 Pitvari sövényhiány (N= 31); Q3830 A nyelv egyéb veleszületett rendellenességei (N= 21); Q6390 A vese veleszületett rendellenessége, k.m.n. (N= 17); Q5520 A here és herezacskó egyéb veleszületett rendellenességei (N= 16); Q6590 A csípő veleszületett deformitása, k.m.n. (N= 14); Q6490 A húgyrendszer rendellenessége, k.m.n. (N= 12); Q8980 Egyéb meghatározott veleszületett rendellenességek (N= 10); **OENO:** 55350 Reconstructio parietis abdominis (N= 37); 55340 Hernioplastica umbilicalis (N= 30).
In the 6th year after pregnancy outcome	297 (cumulative: 27,143)	**BNO:** Q3830 A nyelv egyéb veleszületett rendellenességei (N= 38); Q5560 A hímvessző egyéb veleszületett rendellenességei (N= 20); Q2110 Pitvari sövényhiány (N= 15); Q6390 A vese veleszületett rendellenessége, k.m.n. (N= 14); Q6580 A csípő egyéb veleszületett deformitásai (N= 13); Q6590 A csípő veleszületett deformitása, k.m.n. (N= 11); Q7410 A térd veleszületett rendellenessége (N= 10); **OENO:** 55340 Hernioplastica umbilicalis (N= 35); 55350 Reconstructio parietis abdominis (N= 32).
In the 7th year after pregnancy outcome	305 (cumulative: 27,448)	**BNO:** Q3830 A nyelv egyéb veleszületett rendellenességei (N= 37); Q5560 A hímvessző egyéb veleszületett rendellenességei (N= 19); Q2110 Pitvari sövényhiány (N= 15); Q6390 A vese veleszületett rendellenessége, k.m.n. (N= 14); Q5520 A here és herezacskó egyéb veleszületett rendellenességei (N= 13);

Time periods	No. of children with first report	Relevant BNO / OENO codes in children with first report in this time period
		OENO: 55340 Hernioplastica umbilicalis (N= 42); 55350 Reconstructio parietis abdominis (N= 34).
In the 8th year after pregnancy outcome	158 (cumulative: 27,606)	**BNO:** Q2110 Pitvari sövényhiány (N= 17); Q6390 A vese veleszületett rendellenessége, k.m.n. (N= 15); **OENO: -**
In the 9th year after pregnancy outcome	96 (cumulative: 27,702)	**BNO:** Q2110 Pitvari sövényhiány (N= 13); **OENO: -**

Table 10.E. Temporal pattern of CA codes in cases born in 2005 (Amendment 1).
The total number of evaluable live births was 77,026 in 2005. Only those anomalies reported in the life year of first congenital anomaly report are included.

Time periods	No. of children with first report	Relevant BNO / OENO codes in children with first report in this time period
Up to 365 days after pregnancy outcome	31,791	**BNO:** Q6580 (N=11924); Q6590 (N=4090); Q6560 (N=2914); Q1050 (N=2200); Q2110 (N=2104); Q6500 (N=1647); Q0480 (N=1483); Q6390 (N=1407); Q3810 (N=1043); Q8990 (N=945); Q6550 (N=941); Q3830 (N=847); Q2100 (N=792); Q2500 (N=709); Q6230 (N=705); Q6490 (N=680); Q6800 (N=508); Q6620 (N=487); Q8250 (N=438); Q6510 (N=415); Q6380 (N=380); Q5310 (N=348); Q6520 (N=321); Q2490 (N=320); Q6690 (N=291); Q8280 (N=277); Q6210 (N=243); Q6200 (N=239); Q6600 (N=238); Q3140 (N=236); Q0460 (N=214); Q6680 (N=211); Q6530 (N=201); Q2210 (N=185); Q5400 (N=176); Q4000 (N=169); Q5490 (N=165); O3500 (N=165); Q6640 (N=162); Q3230 (N=161); Q5410 (N=135); Q1030 (N=134); Q0490 (N=131); Q5250 (N=126); Q8330 (N=121); Q6760 (N=105); Q0390 (N=104); Q5320 (N=102); Q5520 (N=96); Q8970 (N=96); Q2560 (N=93); Q6270 (N=91); Q6540 (N=89); Q2120 (N=85); Q6880 (N=81); Q7500 (N=81); Q6000 (N=80); Q6480 (N=79); Q7530 (N=78); Q7750 (N=76); Q7420 (N=75); Q5390 (N=74); Q3210 (N=67); Q6280 (N=67); Q6660 (N=66); Q6610 (N=65); Q02H0 (N=64); Q2480 (N=62); Q8290 (N=59); Q1810 (N=59); Q6990 (N=56); Q8420 (N=53); Q2090 (N=53); Q6900 (N=50); Q3560 (N=49); Q1700 (N=48); Q2510 (N=48); Q7590 (N=47); Q1740 (N=46); Q3690 (N=46); Q8980 (N=44); Q7020 (N=44); Q1800 (N=42); Q6740 (N=42); Q6630 (N=42); Q6190 (N=41); Q7000 (N=40); Q2300 (N=40); Q2130 (N=39); Q2230 (N=38); Q1790 (N=38); Q2790 (N=37); Q1200

Time periods	No. of children with first report	Relevant BNO / OENO codes in children with first report in this time period
		(N=36); Q7090 (N=36); Q3750 (N=36); Q4390 (N=35); Q0400 (N=34); Q1060 (N=34); Q3200 (N=32); Q4310 (N=30); Q2280 (N=30); Q1890 (N=30); Q8220 (N=29); Q6250 (N=29); Q6320 (N=28); Q3820 (N=28); Q2310 (N=28); Q5480 (N=27); Q6310 (N=27); Q0300 (N=27); Q3790 (N=27); Q7490 (N=26); Q3240 (N=26); Q6140 (N=26); Q1880 (N=26); Q3360 (N=25); Q6300 (N=25); Q7130 (N=25); Q4380 (N=24); Q3000 (N=24); Q3800 (N=23); Q4470 (N=23); Q2880 (N=23); Q6020 (N=22); Q7950 (N=21); Q6130 (N=21); Q5010 (N=21); Q6030 (N=21); Q6050 (N=21); Q3860 (N=21); Q7600 (N=20); Q3180 (N=20); Q6700 (N=20); Q2190 (N=20); Q3910 (N=19); Q4210 (N=19); Q1320 (N=19); Q2030 (N=19); Q6650 (N=18); Q5560 (N=18); Q0590 (N=18); Q1690 (N=18); Q2200 (N=18); Q6100 (N=18); Q4200 (N=18); Q7030 (N=18); Q6110 (N=17); Q3540 (N=17); Q6810 (N=17); Q4100 (N=17); Q4220 (N=17); Q2540 (N=17); Q1780 (N=17); Q2330 (N=17); Q6180 (N=17); Q6750 (N=17); Q1000 (N=16); Q3600 (N=16); Q5300 (N=16); Q3780 (N=16); Q8310 (N=16); Q1580 (N=16); Q8480 (N=16); Q3710 (N=16); Q7900 (N=15); Q3700 (N=15); Q7010 (N=15); Q3900 (N=15); Q5500 (N=15); Q3740 (N=15); Q6220 (N=14); Q2570 (N=14); Q1300 (N=14); Q7480 (N=14); Q3120 (N=14); Q4230 (N=14); Q3880 (N=13); Q2890 (N=13); Q3590 (N=13); Q2580 (N=13); Q7510 (N=13); Q8490 (N=13); Q7180 (N=13); Q3850 (N=13); Q2080 (N=13); Q7040 (N=13); Q7580 (N=12); Q3380 (N=12); Q6400 (N=12); Q8700 (N=12); Q8500 (N=12); Q2430 (N=11); Q4420 (N=11); Q3190 (N=11); Q7980 (N=11); Q6910 (N=11); Q2050 (N=11); Q2220 (N=11); Q5290 (N=11); Q7280 (N=11); Q4320 (N=11); Q2400 (N=11); Q3980 (N=10); Q0680 (N=10); Q6920 (N=10); Q1500 (N=10); Q8380 (N=10); Q2340 (N=10); Q0570 (N=10); Q3550 (N=10); Q4180 (N=10); Q2180 (N=10); Q3300 (N=10); **OENO:** 12730 (N=88); 55570 (N=47); 50100 (N=30); 58985 (N=25); 12751 (N=22); 5567B (N=19); 50240 (N=17); 53114 (N=17); 58983 (N=16); 56240 (N=14); 55650 (N=13); 54273 (N=13); 58981 (N=12); 5567A (N=12); 57550 (N=11); 53829 (N=11); 58982 (N=11); 54541 (N=11); 52752 (N=10); 5486A (N=10).
In the 2nd year after pregnancy outcome	1,452 (cumulative: 33,243)	**BNO:** Q6640 Pes calcaneovalgus (N=240); Q6690 A lábak rendellenessége, k.m.n. (N=120); Q5310 Nem descendált here, egyoldali (N=77); Q2110 Pitvari sövényhiány (N=69); Q5250 A szeméremajkak összenövése (N=58); Q6580 A csípő egyéb veleszületett deformitásai (N=55); Q5390 Nem descendált here, k.m.n. (N=46); Q3810 Ankyloglossia (N=45); Q3830 A nyelv egyéb veleszületett rendellenességei (N=37); Q8250 Veleszületett, nem daganatos anyajegy (N=34); Q6660 A láb egyéb veleszületett, valgus jellegű deformitásai (N=34); Q6490 A húgyrendszer rendellenessége, k.m.n. (N=33); Q5320 Nem

Time periods	No. of children with first report	Relevant BNO / OENO codes in children with first report in this time period
		descendált here, kétoldali (N=31); Q6390 A vese veleszületett rendellenessége, k.m.n. (N=30); Q1050 A könnycsatorna veleszületett elzáródása és szűkülete (N=29); Q6680 A láb egyéb veleszületett deformitásai (N=27); Q6590 A csípő veleszületett deformitása, k.m.n. (N=26); Q6760 Pectus excavatum (N=26); Q5520 A here és herezacskó egyéb veleszületett rendellenességei (N=23); Q6560 Instabil csípő (N=22); Q3230 Veleszületett hörgőszűkület (N=21); Q6620 A lábközépcsontok varus állása (N=19); Q5560 A hímvessző egyéb veleszületett rendellenességei (N=18); Q6650 Veleszületett lúdtalp (N=16); Q6380 A vese egyéb meghatározott veleszületett rendellenességei (N=13); Q8220 Mastocytosis (N=13); Q6500 A csípő veleszületett egyoldali dislocatiója (N=12); Q2100 Kamrai sövényhiány (N=12); Q6850 A láb hosszú csontjainak veleszületett, k.m.n. görbülete (N=12); Q6600 Dongaláb (pes equinovarus) (N=11); Q3210 A légcső egyéb veleszületett rendellenességei (N=11); Q2500 Nyitott ductus arteriosus (N=10); Q5410 Hypospadiasis a penisen (N=10). **OENO:** 56240 Orchidopexia (N=27); 55340 Hernioplastica umbilicalis (N=24); 55350 Reconstructio parietis abdominis (N=13).
In the 3rd year after pregnancy outcome	1,047 (cumulative: 34,290)	**BNO:** Q6640 Pes calcaneovalgus (N=350); Q5310 Nem descendált here, egyoldali (N=64); Q5390 Nem descendált here, k.m.n. (N=49); Q6690 A lábak rendellenessége, k.m.n. (N=42); Q5250 A szeméremajkak összenövése (N=42); Q6660 A láb egyéb veleszületett, valgus jellegű deformitásai (N=37); Q2110 Pitvari sövényhiány (N=30); Q6650 Veleszületett lúdtalp (N=27); Q6760 Pectus excavatum (N=24); Q3810 Ankyloglossia (N=22); Q5320 Nem descendált here, kétoldali (N=22); Q3830 A nyelv egyéb veleszületett rendellenességei (N=17); Q6390 A vese veleszületett rendellenessége, k.m.n. (N=17); Q6580 A csípő egyéb veleszületett deformitásai (N=16); Q6490 A húgyrendszer rendellenessége, k.m.n. (N=15); Q8250 Veleszületett, nem daganatos anyajegy (N=10); Q5520 A here és herezacskó egyéb veleszületett rendellenességei (N=10); Q3230 Veleszületett hörgőszűkület (N=10); Q5560 A hímvessző egyéb veleszületett rendellenességei (N=10). **OENO:** 56240 Orchidopexia (N=29); 55350 Reconstructio parietis abdominis (N=28); 55340 Hernioplastica umbilicalis (N=25).
In the 4th year after pregnancy outcome	1,120 (cumulative: 35,410)	**BNO:** Q6640 Pes calcaneovalgus (N=522); Q6660 A láb egyéb veleszületett, valgus jellegű deformitásai (N=47); Q5250 A szeméremajkak összenövése (N=46); Q2110 Pitvari sövényhiány (N=36); Q6760 Pectus excavatum (N=34); Q5310 Nem descendált here, egyoldali (N=33); Q6650 Veleszületett lúdtalp (N=27); Q3810 Ankyloglossia (N=21); Q5560 A hímvessző egyéb veleszületett rendellenességei (N=21); Q3830 A nyelv egyéb veleszületett rendellenességei (N=20); Q5390 Nem

Time periods	No. of children with first report	Relevant BNO / OENO codes in children with first report in this time period
		descendált here, k.m.n. (N=18); Q6690 A lábak rendellenessége, k.m.n. (N=18); Q8250 Veleszületett, nem daganatos anyajegy (N=13); Q6490 A húgyrendszer rendellenessége, k.m.n. (N=12); Q6390 A vese veleszületett rendellenessége, k.m.n. (N=11); Q5320 Nem descendált here, kétoldali (N=10); Q1800 Kopoltyúív eredetű üreg, sipoly, tömlő (N=10). **OENO:** 55350 Reconstructio parietis abdominis (N=44); 55340 Hernioplastica umbilicalis (N=36); 56240 Orchidopexia (N=15).
In the 5th year after pregnancy outcome	795 (cumulative: 36,205)	**BNO:** Q6640 Pes calcaneovalgus (N=343); Q6660 A láb egyéb veleszületett, valgus jellegű deformitásai (N=38); Q6760 Pectus excavatum (N=31); Q2110 Pitvari sövényhiány (N=27); Q5310 Nem descendált here, egyoldali (N=23); Q5250 A szeméremajkak összenövése (N=19); Q3830 A nyelv egyéb veleszületett rendellenességei (N=18); Q3810 Ankyloglossia (N=17); Q6650 Veleszületett lúdtalp (N=16); Q6390 A vese veleszületett rendellenessége, k.m.n. (N=16); Q6690 A lábak rendellenessége, k.m.n. (N=13); Q8250 Veleszületett, nem daganatos anyajegy (N=12); Q5520 A here és herezacskó egyéb veleszületett rendellenességei (N=12); Q5390 Nem descendált here, k.m.n. (N=11); Q6590 A csípő veleszületett deformitása, k.m.n. (N=10). **OENO:** 55350 Reconstructio parietis abdominis (N=29); 55340 Hernioplastica umbilicalis (N=24); 56240 Orchidopexia (N=10).
In the 6th year after pregnancy outcome	829 (cumulative: 37,034)	**BNO:** Q6640 Pes calcaneovalgus (N=421); Q6660 A láb egyéb veleszületett, valgus jellegű deformitásai (N=43); Q6760 Pectus excavatum (N=40); Q3810 Ankyloglossia (N=35); Q3830 A nyelv egyéb veleszületett rendellenességei (N=25); Q6690 A lábak rendellenessége, k.m.n. (N=20); Q6770 Pectus carinatum (N=18); Q5310 Nem descendált here, egyoldali (N=17); Q6650 Veleszületett lúdtalp (N=16); Q2110 Pitvari sövényhiány (N=13); Q5560 A hímvessző egyéb veleszületett rendellenességei (N=13); Q8250 Veleszületett, nem daganatos anyajegy (N=10); Q5390 Nem descendált here, k.m.n. (N=10). **OENO:** 55350 Reconstructio parietis abdominis (N=24); 55340 Hernioplastica umbilicalis (N=24).
In the 7th year after pregnancy outcome	807 (cumulative: 37,841)	**BNO:** Q6640 Pes calcaneovalgus (N=397); Q6760 Pectus excavatum (N=45); Q3830 A nyelv egyéb veleszületett rendellenességei (N=33); Q6660 A láb egyéb veleszületett, valgus jellegű deformitásai (N=23); Q5310 Nem descendált here, egyoldali (N=22); Q3810 Ankyloglossia (N=19); Q2110 Pitvari sövényhiány (N=14); Q6770 Pectus carinatum (N=13); Q5250 A szeméremajkak összenövése (N=12); Q5560 A hímvessző egyéb veleszületett rendellenességei (N=10). **OENO:** 55340 Hernioplastica umbilicalis (N=32); 55350 Reconstructio parietis abdominis (N=24); 56240 Orchidopexia (N=11).

Time periods	No. of children with first report	Relevant BNO / OENO codes in children with first report in this time period
In the 8th year after pregnancy outcome	523 (cumulative: 38,364)	**BNO:** Q6640 Pes calcaneovalgus (N=285); Q6760 Pectus excavatum (N=32); Q5310 Nem descendált here, egyoldali (N=17); Q2110 Pitvari sövényhiány (N=17); Q8250 Veleszületett, nem daganatos anyajegy (N=16); Q6390 A vese veleszületett rendellenessége, k.m.n. (N=12); Q6660 A láb egyéb veleszületett, valgus jellegű deformitásai (N=11); Q6690 A lábak rendellenessége, k.m.n. (N=11); Q3810 Ankyloglossia (N=10).
In the 9th year after pregnancy outcome	390 (cumulative: 38,754)	**BNO:** Q6640 Pes calcaneovalgus (N=210); Q6760 Pectus excavatum (N=18); Q5390 Nem descendált here, k.m.n. (N=14); Q5310 Nem descendált here, egyoldali (N=13); Q2110 Pitvari sövényhiány (N=11).

10.2.4. Time thresholds for redundant reporting of pregnancy outcomes

At study planning, it was recognized that pregnancy outcomes would be detected in a redundant way in most pregnancies, due to multiple relevant code reports with different coding dates but belonging to the same pregnancy outcome. Therefore, redundance removing rules were specified in Protocol Amendment 1, based on biologically plausible intervals between two consecutive pregnancy outcomes of the same kind. The relevance of these biological considerations are visually checked below. It is assumed that redundant codes are temporalily closer to each other, while the independent pregnancy outcomes are temporally not related beyond an initial "recovery" period. Accordingly, the inflexion points of the distribution plots are compared with the pre-specified redundance removing thresholds defined in Protocol Amendment 1 (**Figures 10.C - 10.J**). Note that in these figures, data for N<10 groups was aggregated along the horizontal axis – hence, the number of consecutive pregnancy outcome reports is not necessarily integer, and may be below 1 for some time lag periods.

Figure 10.C. Time threshold for redundant reporting of the same ectopic pregnancy outcome.
EP, ectopic pregnancy.

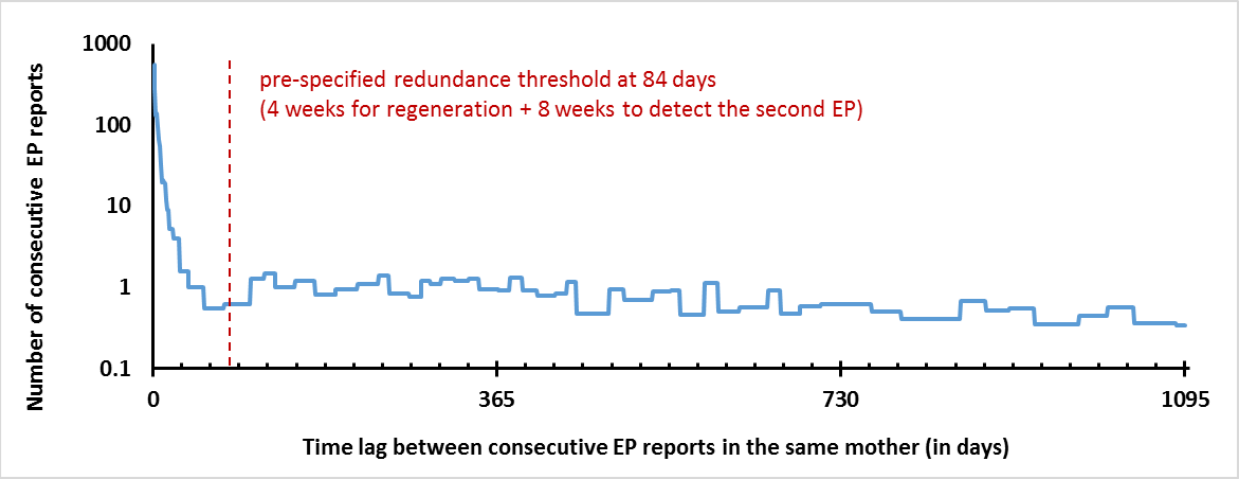


Figure 10.D. Time threshold for redundant reporting of the same spontaneous abortion.
SA, spontaneous abortion.

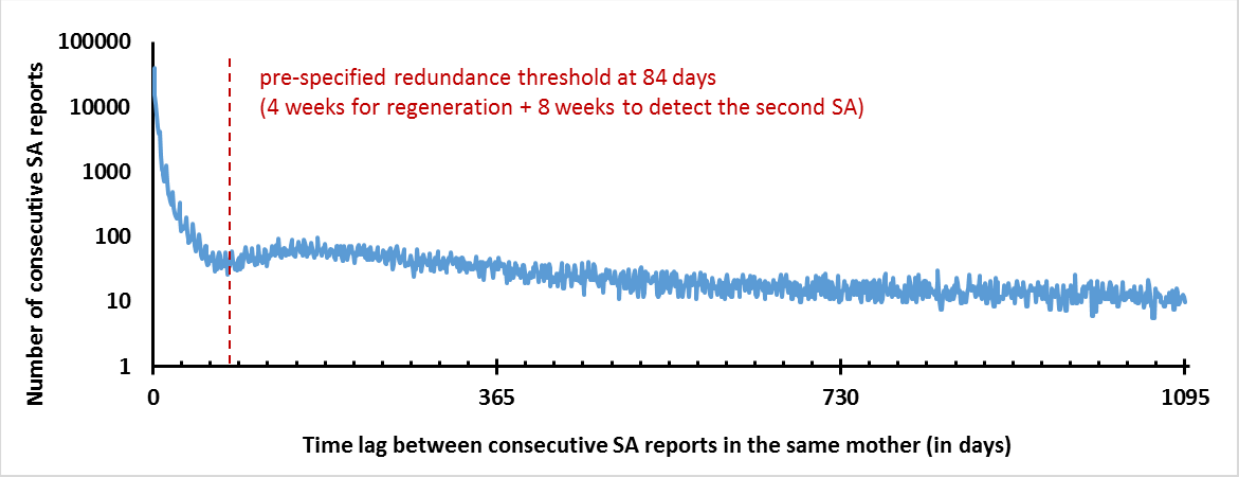


Figure 10.E. Time threshold for redundant reporting of the same ET.
ET, elective termination (no foetal defect or unknown).

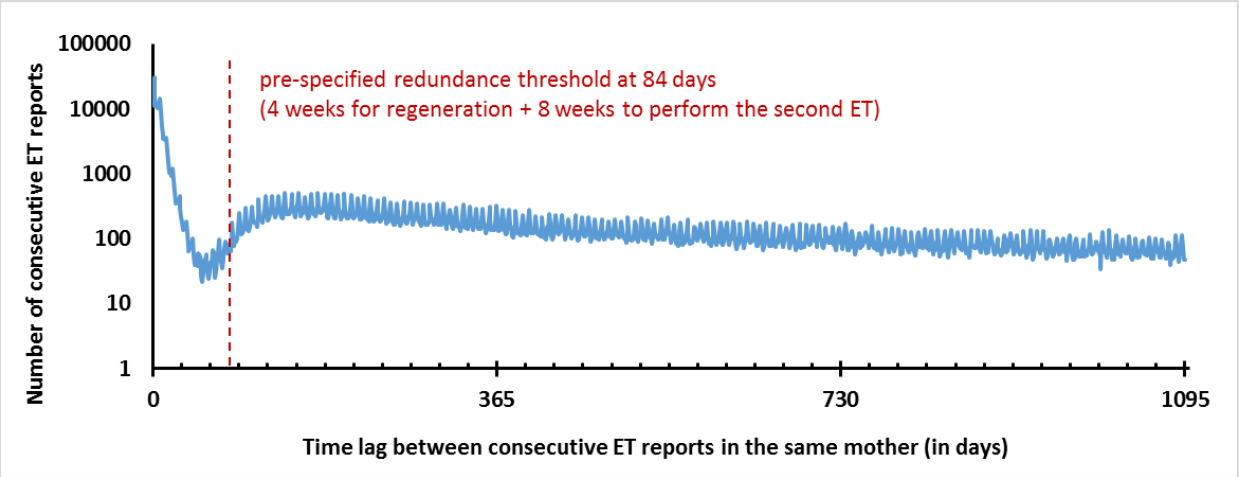


Figure 10.F. Time threshold for redundant reporting of the same ET_FD.
ET_FD, elective termination (foetal defect).

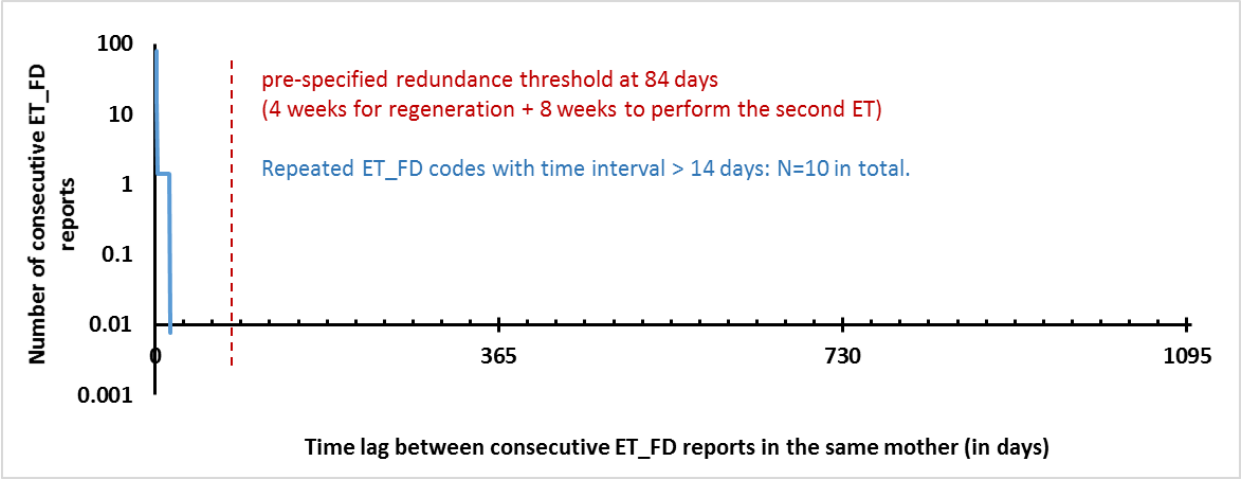


Figure 10.G. Time threshold for redundant reporting of the same SB without foetal defects.
SA, spontaneous abortion; SB, stillbirth without foetal defect.

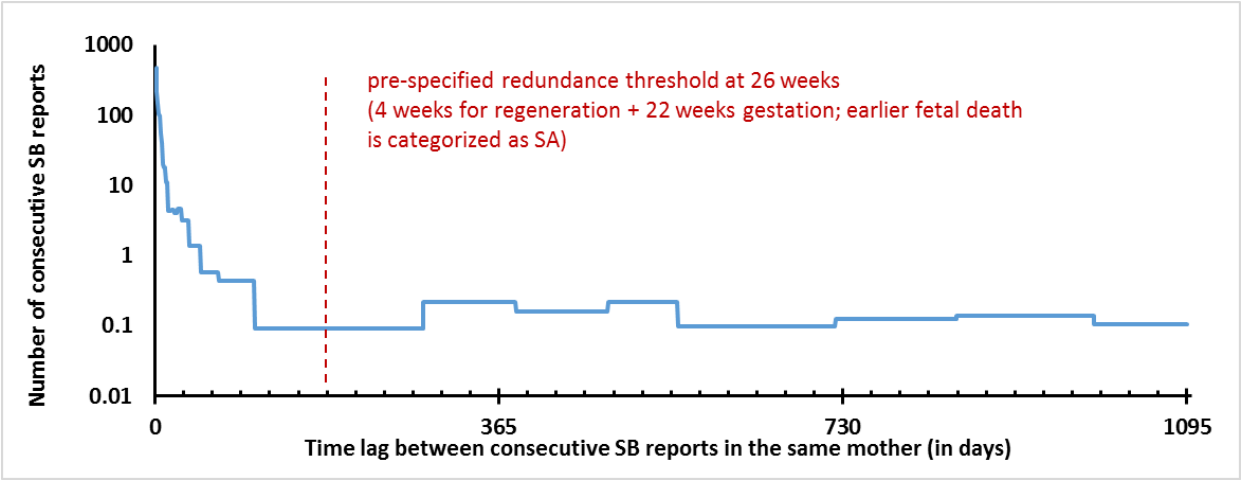


Figure 10.H. Time threshold for redundant reporting of the same SB_FD.
SA, spontaneous abortion; SB_FD, stillbirth with foetal defect.

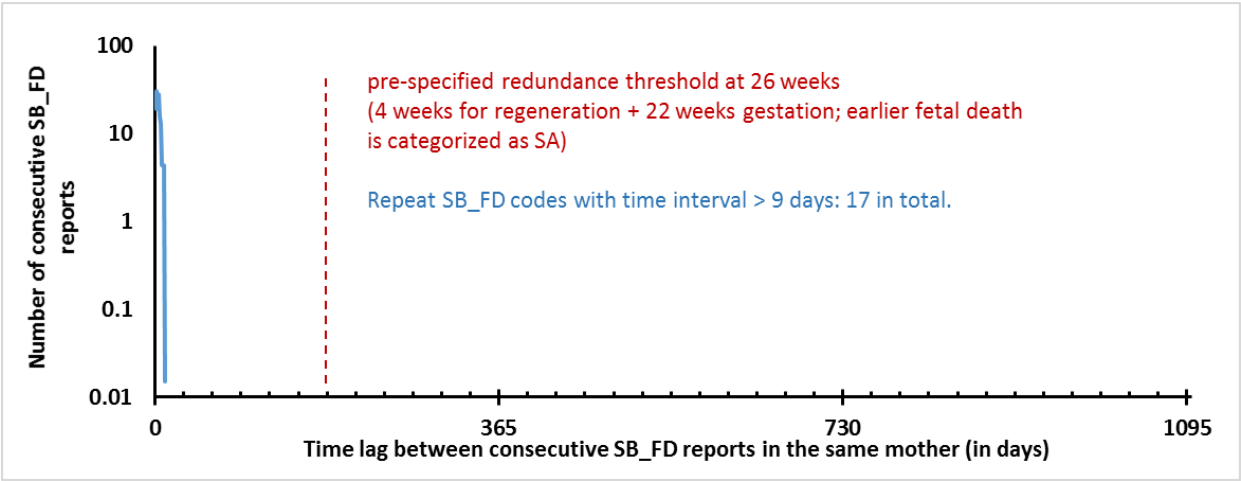


Figure 10.I. Time threshold for redundant reporting of the same LB.
LB, live birth without congenital anomalies.

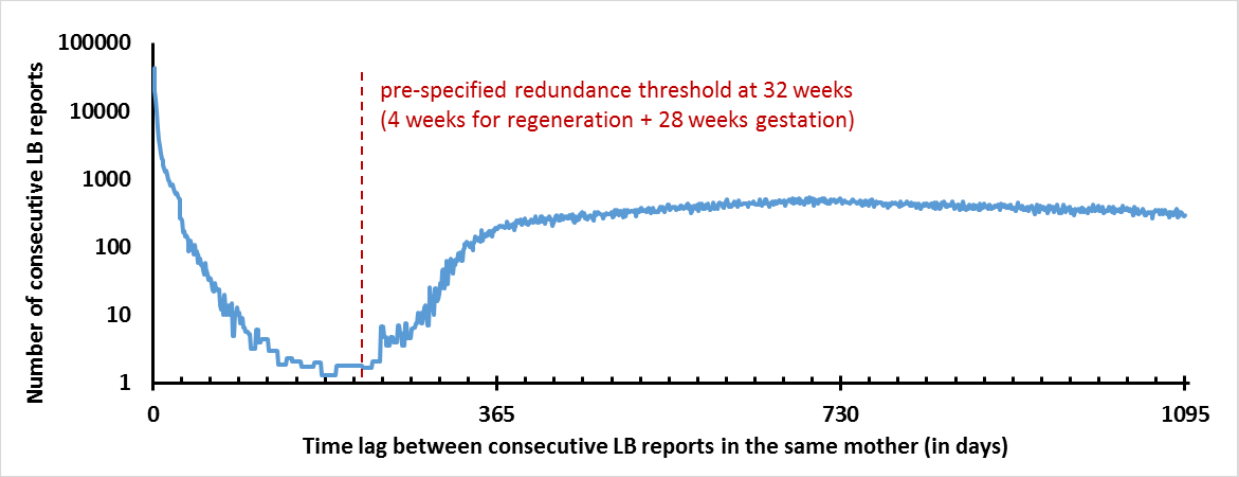
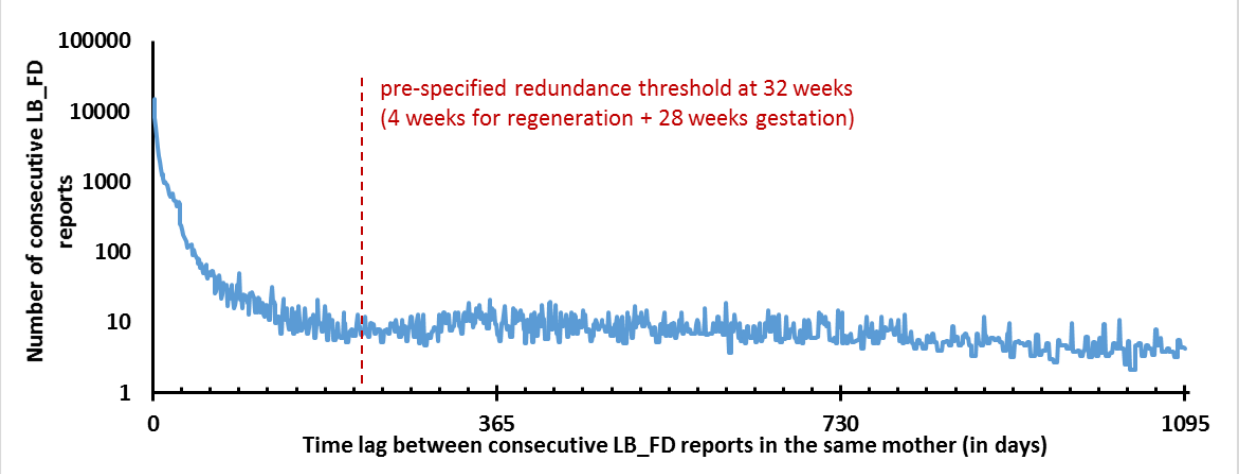


Figure 10.J. Time threshold for redundant reporting of the same LB_FD.
LB_FD, live birth with congenital anomalies.



10.2.5. Descriptive analysis of birth weight data (Amendment 1)

10.2.5.1. Low birthweight (< 2500g) by first trimester drug exposure

Absolute numbers and proportions of low birth-weight cases in drug-exposed and unexposed pregnancies are presented in contingency tables, with pre-planned statistical comparisons (Chi-square test or Fisher's exact test; **Table 10.F**). Birthweight was considered to be <2500g for HBCS codes 15 7110, 15 7120, 15 7130, 15 7140, 15 715Z, 15 7160, 15 7171, 15 7180, 15 719Z, 15 7200, 15 7210, and 15 7220; and at least 2500g for HBCS codes 15 7230, 15 7240, 15 7260, 15 7270, 15 7280, 15 734Z, 15 735Z. Please see Section 9.7.11. of study protocol for the meaning of these HBCS codes. Live births with multiple drug exposures are included.

Table 10.F. Low birthweight rates by first trimester drug exposure (Amendment 1 analysis). Nystatin(local) and miconazole (systemic) are missing from the table due to lack of relevant exposure (see Section 10.3.1).

Drug exposure in first trimester	Low birthweight (< 2500g)	Normal birthweight (≥ 2500g)	Total	P (χ^2)	P (Fischer)
Drug = BUTOCONAZOLE					
All	33,493 (6.83%)	456,549 (93.17%)	490,042 (100%)	$< 10^{-6}$	$< 10^{-6}$
No	33,215 (6.82%)	454,154 (93.18%)	487,369 (100%)		
Yes	278 (10.40%)	2,395 (89.60%)	2,673 (100%)		
Drug = CLOTRIMAZOLE					
All	33,493 (6.83%)	456,549 (93.17%)	490,042 (100%)	$< 10^{-6}$	$< 10^{-6}$
No	32,823 (6.86%)	445,325 (93.14%)	478,148 (100%)		
Yes	670 (5.63%)	11,224 (94.37%)	11,894 (100%)		
Drug = METRONIDAZOLE (local)					
All	33,493 (6.83%)	456,549 (93.17%)	490,042 (100%)	$< 10^{-6}$	$< 10^{-6}$
No	32,829 (6.81%)	449,411 (93.19%)	482,240 (100%)		
Yes	664 (8.51%)	7,138 (91.49%)	7,802 (100%)		
Drug = METRONIDAZOLE (systemic)					
All	33,493 (6.83%)	456,549 (93.17%)	490,042 (100%)	0.358	0.351
No	33,332 (6.83%)	454,513 (93.17%)	487,845 (100%)		
Yes	161 (7.33%)	2,036 (92.67%)	2,197 (100%)		
Drug = MICONAZOLE (local)					
All	33,493 (6.83%)	456,549 (93.17%)	490,042 (100%)	$< 10^{-6}$	$< 10^{-6}$
No	32,848 (6.81%)	449,600 (93.19%)	482,448 (100%)		
Yes	645 (8.49%)	6,949 (91.51%)	7,594 (100%)		
Drug = NYSTATIN (systemic)					
All	33,493 (6.83%)	456,549 (93.17%)	490,042 (100%)	0.306	0.242
No	33,490 (6.83%)	456,527 (93.17%)	490,017 (100%)		
Yes	3 (12.00%)	22 (88.00%)	25 (100%)		

10.2.5.2. Low birthweight HBCS sub-categories by first trimester drug exposure

Absolute and relative proportions of various low birth-weight cases in drug-exposed and unexposed pregnancies in first trimester are presented in contingency tables, with pre-planned statistical comparisons (Chi-square test; **Table 10.G**). Birthweight was considered to be 0-1000g for HBCS 157110; 1000-1499g for HBCS 157120 and 157130; 1500-1999g for HBCS 157140,

15715Z, 157160, 157170; 2000-2499g for HBCS 157180, 15719Z, 157200, 157210, 15 7220; and >2500g for HBCS codes 157230, 157240, 157260, 157270, 157280, 15734Z, and 15735Z, respectively. Please see Section 9.7.11. of study protocol for the meaning of these HBCS codes. Live births with multiple drug exposures are included.

Table 10.G. Low birthweight sub-category rates by first trimester drug exposure (Amendment 1 analysis). Nystatin(local) and miconazole (systemic) are missing from the table due to lack of relevant exposure (see Section 10.3.1).

Drug exposure in first trimester	Birthweight based on the reported HBCS codes						
	0-1000g	1000-1499g	1500-1999g	2000-2499g	2500g-	Total	χ^2 P value
Drug = BUTOCONAZOLE							
All	1,806 (0.37%)	3,262 (0.67%)	7,307 (1.49%)	21,118 (4.31%)	456,549 (93.17%)	490,042 (100.00%)	
No	1,795 (0.37%)	3,234 (0.66%)	7,224 (1.48%)	20,962 (4.30%)	454,154 (93.18%)	487,369 (100.00%)	$<10^{-6}$
Yes	11 (0.41%)	28 (1.05%)	83 (3.11%)	156 (5.84%)	2,395 (89.60%)	2,673 (100.00%)	
Drug = CLOTRIMAZOLE							
All	1,806 (0.37%)	3,262 (0.67%)	7,307 (1.49%)	21,118 (4.31%)	456,549 (93.17%)	490,042 (100.00%)	
No	1,774 (0.37%)	3,185 (0.67%)	7,169 (1.50%)	20,695 (4.33%)	445,325 (93.14%)	478,148 (100.00%)	$<10^{-5}$
Yes	32 (0.27%)	77 (0.65%)	138 (1.16%)	423 (3.56%)	11,224 (94.37%)	11,894 (100.00%)	
Drug = METRONIDAZOLE (local)							
All	1,806 (0.37%)	3,262 (0.67%)	7,307 (1.49%)	21,118 (4.31%)	456,549 (93.17%)	490,042 (100.00%)	
No	1,784 (0.37%)	3,178 (0.66%)	7,148 (1.48%)	20,719 (4.30%)	449,411 (93.19%)	482,240 (100.00%)	$<10^{-6}$
Yes	22 (0.28%)	84 (1.08%)	159 (2.04%)	399 (5.11%)	7,138 (91.49%)	7,802 (100.00%)	
Drug = METRONIDAZOLE (systemic)							
All	1,806 (0.37%)	3,262 (0.67%)	7,307 (1.49%)	21,118 (4.31%)	456,549 (93.17%)	490,042 (100.00%)	
No	1,799 (0.37%)	3,249 (0.67%)	7,278 (1.49%)	21,006 (4.31%)	454,513 (93.17%)	487,845 (100.00%)	0.426
Yes	0 (0.00%)	13 (0.59%)	29 (1.32%)	112 (5.10%)	2,036 (92.67%)	2,197 (100.00%)	
Drug = MICONAZOLE (local)							
All	1,806 (0.37%)	3,262 (0.67%)	7,307 (1.49%)	21,118 (4.31%)	456,549 (93.17%)	490,042 (100.00%)	
No	1,785 (0.37%)	3,180 (0.66%)	7,151 (1.48%)	20,732 (4.30%)	449,600 (93.19%)	482,448 (100.00%)	$<10^{-6}$
Yes	21 (0.28%)	82 (1.08%)	156 (2.05%)	386 (5.08%)	6,949 (91.51%)	7,594 (100.00%)	
Drug = NYSTATIN (systemic)							
All	1,806 (0.37%)	3,262 (0.67%)	7,307 (1.49%)	21,118 (4.31%)	456,549 (93.17%)	490,042 (100.00%)	$<10^{-6}$

No	1,804 (0.37%)	3,262 (0.67%)	7,307 (1.49%)	21,117 (4.31%)	456,527 (93.17%)	490,017 (100.00%)	
Yes	2 (8.00%)	0 (0.00%)	0 (0.00%)	1 (4.00%)	22 (88.00%)	25 (100.00%)	

10.2.5.3. Reported exact birth-weight data by first trimester drug exposure

Exact birthweight data was reported for 99.37% of all live births included in this study, and for at least 99% of births in all subgroups with various first trimester drug exposures. Mean birthweight data in grams with it's 95% confidence interval is shown in **Table 10.H**.

Table 10.H. Reported birthweight by drug exposure in first trimester (Amendment 1 analysis). Nystatin(local) and miconazole (systemic) are missing from the table due to lack of relevant exposure (see Section 10.3.1).

		Individual birth weight data in the OEP database			
		Not reported	Reported	Mean	95% CI
Drug exposure in first trimester	butoconazole	23 (0.85%)	2680 (99.15%)	3,259 g	3,235 – 3,282 g
	clotrimazole	105 (0.87%)	11,908 (99.13%)	3,343 g	3,333 – 3,352 g
	miconazole (local)	40 (0.52%)	7,608 (99.48%)	3,272 g	3,259 – 3,286 g
	metronidazole (local)	42 (0.53%)	7818 (99.47%)	3,271 g	3,257 – 3,284 g
	metronidazole (systemic)	18 (0.81%)	2,200 (99.19%)	3,278 g	3,255 – 3,302 g
	nystatin (systemic)	0 (0.00%)	25 (100.00%)	3,285 g	2,919 - 3,651 g
	none	2,952 (0.63%)	467,074 (99.37%)	3,311 g	3,310 – 3,313 g
	total	3,120 (0.63%)	490,415 (99.37%)	3,311 g	3,309 – 3,313 g

For discussion of findings, please see Section 11.

10.2.6. Descriptive comparison of butoconazole and clotrimazole exposed pregnancies in Amendment 2 regression models on low birthweight

Due to the quasi-randomized design of these analyses, butoconazole and clotrimazole exposed pregnancies of identical micro-regional socioeconomic status are expected to be similar in all measured and unmeasured variables. For a descriptive comparison of selected measurable predictors of low birthweight, please see Table 10.I. For study design details, please see Section 9.1.3. No clear trends were observed in these descriptive analyses, butoconazole and clotrimazole exposed pregnancies were similar in general.

Table 10.I. Comparison of butoconazole and clotrimazole exposed pregnancies in Amendment 2 models on low birthweight.

	B_{11+} = yes	**C_{11+} = yes**	**B_{D1+} = yes**	**C_{D1+} = yes**	**B_{D1+} and C_{D1+} = no**
Maternal residence: **rural, in most deprived areas requiring complex intervention**					
number of live births (N)	10	74	42	390	23 818
maternal age (mean; SD)	28.35 4.38	27.33 5.64	27.88 5.33	27.01 5.56	26.29 5.9
infant sex: male (N, %)	<10	43 58.11%	21 50%	199 51.03%	12 450 52.27%
evidence of miscarriage in the last 4 years* (N, %)	<10	<10	<10	52 13.33%	2 929 12.3%
evidence of at least 1 prior birth in the last 4 years* (N, %)	<10	14 18.92%	13 30.95%	101 25.9%	8 869 37.24%
evidence of at least 1 low birthweight (<2500g) infant in the last 4 years (N, %)	<10	<10	<10	<10	362 1.52%
history of maternal diabetes* (N, %)	<10	<10	<10	28 7.18%	1 089 4.57%
number of maternal gynecology visits in first trimester** (mean, SD, median, IQR)	3.4 2.32 3 1.75	2.43 1.66 2 2	2.52 2.3 2 2	2.35 1.87 2 2	1.98 1.81 2 2
Maternal residence: **urban, in most deprived areas requiring complex intervention**					
number of live births (N)	<10	38	34	229	11 162
maternal age (mean; SD)	28.31 4.43	27.89 4.68	27.94 4.9	28.28 4.62	27.93 5.29
infant sex: male (N, %)	<10	23 60.53%	19 55.88%	124 54.15%	5 791 51.88%
evidence of miscarriage in the last 4 years* (N, %)	<10	<10	<10	26 11.35%	1 282 11.49%
evidence of at least 1 prior birth in the last 4 years* (N, %)	<10	<10	<10	53 23.14%	3 230 28.94%
evidence of at least 1 low birthweight (<2500g) infant in the last 4 years (N, %)	<10	<10	<10	<10	109 0.98%
history of maternal diabetes* (N, %)	<10	<10	<10	11 4.8%	566 5.07%

number of maternal gynecology visits in first trimester** (mean, SD, median, IQR)	3 2.31 3 3	3.03 1.65 3 2	2.59 2.16 2 2	2.53 2.06 2 3	2.52 2.13 2 3
Maternal residence: **rural, in most deprived areas not requiring complex intervention**					
number of live births (N)	<10	33	24	200	9 034
maternal age (mean; SD)	28.98 4.31	25.17 4.44	28.38 5.87	26.71 5.44	26.88 5.81
infant sex: male (N, %)	<10	17 51.52%	13 54.17%	109 54.5%	4 686 51.87%
evidence of miscarriage in the last 4 years* (N, %)	<10	<10	<10	13 6.5%	1 063 11.77%
evidence of at least 1 prior birth in the last 4 years* (N, %)	<10	<10	<10	42 21%	3 352 37.1%
evidence of at least 1 low birthweight (<2500g) infant in the last 4 years (N, %)	<10	<10	<10	<10	112 1.24%
history of maternal diabetes* (N, %)	<10	<10	<10	13 6.5%	582 6.44%
number of maternal gynecology visits in first trimester** (mean, SD, median, IQR)	2.83 0.75 3 0.75	2.85 1.87 2 3	2.38 1.64 2 2.25	2.49 2.01 2 2.25	2.22 1.98 2 2
Maternal residence: **urban, in most deprived areas not requiring complex intervention**					
number of live births (N)	10	54	51	318	11 724
maternal age (mean; SD)	30.28 3.7	28.8 4.97	29.37 3.98	28.33 4.63	27.79 5.42
infant sex: male (N, %)	<10	29 53.7%	26 50.98%	153 48.11%	6 230 53.14%
evidence of miscarriage in the last 4 years* (N, %)	<10	<10	<10	40 12.58%	1 338 11.41%
evidence of at least 1 prior birth in the last 4 years* (N, %)	<10	20 37.04%	12 23.53%	98 30.82%	3 752 32%
evidence of at least 1 low birthweight (<2500g) infant in the last 4 years (N, %)	<10	<10	<10	<10	101 0.86%
history of maternal diabetes* (N, %)	<10	<10	<10	20 6.29%	666 5.68%
number of maternal gynecology visits in first trimester** (mean, SD, median, IQR)	2.5 1.9 2.5 2	4.28 2.96 4 2	3.43 2.65 3 3	3.09 2.55 3 3	2.77 2.5 2 3
Maternal residence: **rural, in deprived areas (not including the most deprived areas)**					
number of live births (N)	24	85	157	621	31 633
maternal age (mean; SD)	28.38 4.36	27.73 4.44	28.05 4.31	27.71 5.4	27.72 5.45
infant sex: male (N, %)	11 45.83%	41 48.24%	74 47.13%	320 51.53%	16 449 52%

evidence of miscarriage in the last 4 years* (N, %)	<10	<10	13 8.28%	64 10.31%	3 675 11.62%
evidence of at least 1 prior birth in the last 4 years* (N, %)	<10	19 22.35%	62 39.49%	174 28.02%	9 763 30.86%
evidence of at least 1 low birthweight (<2500g) infant in the last 4 years (N, %)	<10	<10	<10	<10	223 0.7%
history of maternal diabetes* (N, %)	<10	<10	14 8.92%	25 4.03%	2 010 6.35%
number of maternal gynecology visits in first trimester** (mean, SD, median, IQR)	3.13 2.27 3 3.25	2.99 1.81 3 2	2.56 2.27 2 3	2.36 1.93 2 2	2.3 1.91 2 2
Maternal residence: **urban, in deprived areas (not including the most deprived areas)**					
number of live births (N)	51	115	301	660	29 758
maternal age (mean; SD)	28.35 4.72	28.1 3.78	28.2 5.25	28.54 4.59	28.72 5.08
infant sex: male (N, %)	22 43.14%	62 53.91%	156 51.83%	342 51.82%	15 438 51.88%
evidence of miscarriage in the last 4 years* (N, %)	<10	14 12.17%	32 10.63%	92 13.94%	3 563 11.97%
evidence of at least 1 prior birth in the last 4 years* (N, %)	12 23.53%	20 17.39%	71 23.59%	168 25.45%	8 578 28.83%
evidence of at least 1 low birthweight (<2500g) infant in the last 4 years (N, %)	<10	<10	<10	<10	151 0.51%
history of maternal diabetes* (N, %)	<10	<10	23 7.64%	44 6.67%	1 975 6.64%
number of maternal gynecology visits in first trimester** (mean, SD, median, IQR)	4.43 2.51 4 3	3.68 2.74 3 3.5	3.54 2.51 3 3	2.99 2.46 3 3	2.95 2.32 3 3
Maternal residence: **rural, in not deprived areas**					
number of live births (N)	118	336	520	2 119	82 161
maternal age (mean; SD)	29.58 4.2	28.95 4.35	29.6 4.41	29.08 4.76	29.02 4.92
infant sex: male (N, %)	55 46.61%	193 57.44%	261 50.19%	1 105 52.15%	42 619 51.87%
evidence of miscarriage in the last 4 years* (N, %)	20 16.95%	42 12.5%	62 11.92%	250 11.8%	9 915 12.07%
evidence of at least 1 prior birth in the last 4 years* (N, %)	38 32.2%	89 26.49%	156 30%	650 30.67%	26 988 32.85%
evidence of at least 1 low birthweight (<2500g) infant in the last 4 years (N, %)	<10	<10	<10	<10	385 0.47%
history of maternal diabetes* (N, %)	12 10.17%	13 3.87%	40 7.69%	143 6.75%	6 510 7.92%

number of maternal gynecology visits in first trimester** (mean, SD, median, IQR)	2.81 2.35 2 3	2.73 2.12 2 3	2.29 2.01 2 2	2.2 2.05 2 2	2.19 1.93 2 2
Maternal residence: **urban, in not deprived areas**					
number of live births (N)	371	1 141	1 684	7 130	226 190
maternal age (mean; SD)	30.59 4.14	30.03 4.03	30.12 4.3	30.05 4.42	30.03 4.62
infant sex: male (N, %)	192 51.75%	603 52.85%	898 53.33%	3 683 51.65%	116 872 51.67%
evidence of miscarriage in the last 4 years* (N, %)	43 11.59%	147 12.88%	215 12.77%	821 11.51%	27 374 12.1%
evidence of at least 1 prior birth in the last 4 years* (N, %)	87 23.45%	303 26.56%	480 28.5%	2 033 28.51%	67 584 29.88%
evidence of at least 1 low birthweight (<2500g) infant in the last 4 years (N, %)	<10	<10	<10	28 0.39%	937 0.41%
history of maternal diabetes* (N, %)	36 9.7%	80 7.01%	125 7.42%	511 7.17%	17 439 7.71%
number of maternal gynecology visits in first trimester** (mean, SD, median, IQR)	3.2 2.41 3 4	3.1 2.42 3 4	2.58 2.22 2 3	2.74 2.3 2 3	2.45 2.14 2 3

*criteria: see at Protocol Amendment 2 Annex 3.4.2. IQR, interquartile range. ** Definition of maternal gynecology visits: outpatient visit at a gynaecologist; or outpatient visit due to pregnancy-related disease/condition (as specified in Section 9.8.2); or hospitalization due to pregnancy-related disease/condition. Hospitalization is calculated as a single gynecology visit, irrespective of hospitalization duration. The maximal number of calculated gynecology visits per day is 1. B11+, at least one butroconazole prescription in the first trimester. C11+, at least one clotrimazole prescription in the first trimester. BD1+, at least one butroconazole prescription during pregnancy. CD1+, at least one clotrimazole prescription during pregnancy.

10.3. Outcome data

This was the first study with the intention to determine pregnancy outcomes, pregnancy periods, drug exposure, pregnancy risks and confounding factors solely from the OEP database. In this pioneering exercise, the original study protocol failed to identify most mother – offspring pairs, since it did not match the transient and permanent social security numbers of the investigated children, resulting in the loss of medical follow-up of about 440 000 live births. Moreover, the exact hierarchy of rules for redundant and conflicting pregnancy outcome codes has not been defined in the original protocol, making pregnancy outcomes ambiguous in cases with multiple outcome records. Accordingly, as justified in Protocol Amendment 2, the study has not been analysed as planned in the original protocol. Instead, all descriptive statistics and statistical analyses (including the sensitivity analyses) are conducted according to Protocol Amendment 2 and Protocol Amendment 1.

10.3.1. Summary table of pregnancy outcomes: Amendment 2 analysis

Definition of outcome categories and drug exposure periods follow the relevant CHMP recommendations {EMEA/CHMP, 2005 #17}. In Amendment 2 analyses, "Elective termination (foetal defects)" and "Stillbirth with foetal defects" pregnancy outcomes were not found, due to the applied EUROCAT definitions (which focused on codes typically reported after live birth). Amendment 2 outcomes by drug exposure are shown in **Tables 10.J -10.M.**

In OEP database analysis results, all values are missing for N<10 patient groups. In the presented tables below, missing values of exposed sample sizes ("E" columns) were calculated as the number of unexposed pregnancies substracted from the total number of pregnancies with the same outcome. It is apparent that none of the pregnancies was exposed to systemic miconazole, local nystatin, or local naproxen in this study. All together, 7 pregnancies were exposed to rofecoxib (2 elective terminations without known foetal defects, 1 live birth with congenital anomaly, 4 live births without congenital anomaly); and 6 pregnancies were exposed to local ibuprophen (2 spontaneous abortions, 1 elective termination without known foetal defects, 1 live birth without congenital anomaly, and 2 unidentified / unknown outcomes).

Table 10.J. Pregnancy outcomes by butoconazole exposure (Amendment 2 analysis).
B, Before pregnancy; T1, first trimester; T2-T3, after first trimester; D, during all pregnancy; U, unknown; E, all exposed cases; N, non-exposed cases; All, all cases.

Pregnancy outcomes	Timing of butoconazole exposure in pregnancy							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy					52	52	10,502	10,554
Spontaneous abortion					1,109	1,109	127,047	128,156
Elective termination (no foetal defects or unknown)					1,734	1,734	299,359	301,093
Stillbirth without foetal defects		14	18			36	3,340	3,376
Live birth with congenital anomaly	557	823	2,428	81		3,697	147,578	151,275
Live birth without congenital anomaly	1,060	1,879	5,529	226		8,136	334,124	342,260
Unidentified / unknown outcome					2,178	2,178	159,897	162,075

Table 10.K. Pregnancy outcomes by exposure to therapeutic controls (Amendment 2 analysis).
B, Before pregnancy; T1, first trimester; T2-T3, after first trimester; D, during all pregnancy; U, unknown; E, all exposed cases; N, non-exposed cases; All, all cases.

Pregnancy outcomes	Timing of clotrimazole exposure in pregnancy							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy					62	62	10,492	10,554
Spontaneous abortion					2,402	2,402	125,754	128,156
Elective termination (no foetal defects or unknown)					4,083	4,083	297,010	301,093
Stillbirth without foetal defects		55	232	18		275	3,101	3,376
Live birth with congenital anomaly	703	3,789	17,274	1,163		20,364	130,911	151,275
Live birth without congenital anomaly	1,390	8,230	38,633	2,655		45,130	297,130	342,260
Unidentified / unknown outcome					4,006	4,006	158,069	162,075
Pregnancy outcomes	**Timing of metronidazole_local exposure in pregnancy**							
	B	**T1**	**T2-T3**	**D**	**U**	**E**	**N**	**All**
Ectopic pregnancy					149	149	10,405	10,554
Spontaneous abortion					3,333	3,333	124,823	128,156
Elective termination (no foetal defects or unknown)					8,047	8,047	293,046	301,093
Stillbirth without foetal defects	15	53	255			313	3,063	3,376
Live birth with congenital anomaly	1,076	2,489	19,379	608		22,080	129,195	151,275
Live birth without congenital anomaly	2,297	5,370	43,495	1,348		49,317	292,943	342,260
Unidentified / unknown outcome					6,685	6,685	155,390	162,075

Pregnancy outcomes	Timing of metronidazole_systemic exposure in pregnancy							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy					140	140	10,414	10,554
Spontaneous abortion					1,775	1,775	126,381	128,156
Elective termination (no foetal defects or unknown)					4,964	4,964	296,129	301,093
Stillbirth without foetal defects		17	35			56	3,320	3,376
Live birth with congenital anomaly	567	714	2,103	43		3,304	147,971	151,275
Live birth without congenital anomaly	1,174	1,506	4,383	81		6,913	335,347	342,260
Unidentified / unknown outcome					3,895	3,895	158,180	162,075

Pregnancy outcomes	Timing of miconazole_local exposure in pregnancy							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy					142	142	10,412	10,554
Spontaneous abortion					3,176	3,176	124,980	128,156
Elective termination (no foetal defects or unknown)					7,599	7,599	293,494	301,093
Stillbirth without foetal defects	15	52	241			300	3,076	3,376
Live birth with congenital anomaly	1,034	2,440	18,417	578		21,068	130,207	151,275
Live birth without congenital anomaly	2,230	5,207	41,855	1,273		47,538	294,722	342,260
Unidentified / unknown outcome					6,089	6,089	155,986	162,075

Pregnancy outcomes	Timing of miconazole_systemic exposure in pregnancy							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy						0	10,554	10,554
Spontaneous abortion						0	128,156	128,156
Elective termination (no foetal defects or unknown)						0	301,093	301,093
Stillbirth without foetal defects						0	3,376	3,376
Live birth with congenital anomaly						0	151,275	151,275
Live birth without congenital anomaly						0	342,260	342,260
Unidentified / unknown outcome						0	162,075	162,075
Pregnancy outcomes	**Timing of nystatin_local exposure in pregnancy**							
	B	**T1**	**T2-T3**	**D**	**U**	**E**	**N**	**All**
Ectopic pregnancy						0	10,554	10,554
Spontaneous abortion						0	128,156	128,156
Elective termination (no foetal defects or unknown)						0	301,093	301,093
Stillbirth without foetal defects						0	3,376	3,376
Live birth with congenital anomaly						0	151,275	151,275
Live birth without congenital anomaly						0	342,260	342,260
Unidentified / unknown outcome						0	162,075	162,075

Pregnancy outcomes	Timing of nystatin_systemic exposure in pregnancy							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy						0	10,554	10,554
Spontaneous abortion					15	15	128,141	128,156
Elective termination (no foetal defects or unknown)					23	23	301,070	301,093
Stillbirth without foetal defects						0	3,376	3,376
Live birth with congenital anomaly		11	11			25	151,250	151,275
Live birth without congenital anomaly	10	14	30			52	342,208	342,260
Unidentified / unknown outcome					26	26	162,049	162,075

Table 10.L. Pregnancy outcomes by exposure to active controls in spontaneous abortion models (Amendment 2 analysis).

B, Before pregnancy; T1, first trimester; T2-T3, after first trimester; D, during all pregnancy; U, unknown; E, all exposed cases; N, non-exposed cases; All, all cases.

Pregnancy outcomes	Timing of celecoxib exposure in pregnancy							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy						0	10,554	10,554
Spontaneous abortion						3	128,153	128,156
Elective termination (no foetal defects or unknown)					11	11	301,082	301,093
Stillbirth without foetal defects						0	3,376	3,376
Live birth with congenital anomaly						7	151,268	151,275
Live birth without congenital anomaly						9	342,251	342,260
Unidentified / unknown outcome					32	32	162,043	162,075

Pregnancy outcomes	Timing of diclofenac_local exposure in pregnancy							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy					18	18	10,536	10,554
Spontaneous abortion					428	428	127,728	128,156
Elective termination (no foetal defects or unknown)					1,177	1,177	299,916	301,093
Stillbirth without foetal defects		10				14	3,362	3,376
Live birth with congenital anomaly	107	194	295	37		531	150,744	151,275
Live birth without congenital anomaly	229	472	624	89		1,180	341,080	342,260
Unidentified / unknown outcome					1,564	1,564	160,511	162,075

Pregnancy outcomes	Timing of diclofenac_systemic exposure in pregnancy							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy					406	406	10,148	10,554
Spontaneous abortion					6,139	6,139	122,017	128,156
Elective termination (no foetal defects or unknown)					15,698	15,698	285,395	301,093
Stillbirth without foetal defects	37	96	48			166	3,210	3,376
Live birth with congenital anomaly	2,609	3,616	2,006	301		7,543	143,732	151,275
Live birth without congenital anomaly	5,731	7,966	4,617	634		16,794	325,466	342,260
Unidentified / unknown outcome					13,341	13,341	148,734	162,075

Pregnancy outcomes	Timing of ibuprofen_local exposure in pregnancy							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy						0	10,554	10,554
Spontaneous abortion						2	128,154	128,156
Elective termination (no foetal defects or unknown)						1	301,092	301,093
Stillbirth without foetal defects						0	3,376	3,376
Live birth with congenital anomaly						0	151,275	151,275
Live birth without congenital anomaly						1	342,259	342,260
Unidentified / unknown outcome						2	162,073	162,075

Pregnancy outcomes	Timing of ibuprofen_systemic exposure in pregnancy							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy						2	10,552	10,554
Spontaneous abortion					30	30	128,126	128,156
Elective termination (no foetal defects or unknown)					75	75	301,018	301,093
Stillbirth without foetal defects						1	3,375	3,376
Live birth with congenital anomaly	20	24				47	151,228	151,275
Live birth without congenital anomaly	29	48	22			99	342,161	342,260
Unidentified / unknown outcome					61	61	162,014	162,075

Pregnancy outcomes	Timing of indomethacin_local exposure in pregnancy							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy						1	10,553	10,554
Spontaneous abortion						2	128,154	128,156
Elective termination (no foetal defects or unknown)						4	301,089	301,093
Stillbirth without foetal defects						0	3,376	3,376
Live birth with congenital anomaly						3	151,272	151,275
Live birth without congenital anomaly			12			20	342,240	342,260
Unidentified / unknown outcome						7	162,068	162,075

Pregnancy outcomes	Timing of indomethacin_systemic exposure in pregnancy							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy						4	10,550	10,554
Spontaneous abortion					76	76	128,080	128,156
Elective termination (no foetal defects or unknown)					175	175	300,918	301,093
Stillbirth without foetal defects						2	3,374	3,376
Live birth with congenital anomaly	20	34	42			90	151,185	151,275
Live birth without congenital anomaly	52	66	84			196	342,064	342,260
Unidentified / unknown outcome					253	253	161,822	162,075

Pregnancy outcomes	Timing of naproxen_local exposure in pregnancy							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy						0	10,554	10,554
Spontaneous abortion						0	128,156	128,156
Elective termination (no foetal defects or unknown)						0	301,093	301,093
Stillbirth without foetal defects						0	3,376	3,376
Live birth with congenital anomaly						0	151,275	151,275
Live birth without congenital anomaly						0	342,260	342,260
Unidentified / unknown outcome						0	162,075	162,075

Pregnancy outcomes	Timing of naproxen_systemic exposure in pregnancy							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy					158	158	10,396	10,554
Spontaneous abortion					1,242	1,242	126,914	128,156
Elective termination (no foetal defects or unknown)					2,830	2,830	298,263	301,093
Stillbirth without foetal defects		15				27	3,349	3,376
Live birth with congenital anomaly	451	599	193	32		1,161	150,114	151,275
Live birth without congenital anomaly	873	1,144	409	70		2,270	339,990	342,260
Unidentified / unknown outcome					3,707	3,707	158,368	162,075

Pregnancy outcomes	Timing of rofecoxib exposure in pregnancy							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy						0	10,554	10,554
Spontaneous abortion						0	128,156	128,156
Elective termination (no foetal defects or unknown)						2	301,091	301,093
Stillbirth without foetal defects						0	3,376	3,376
Live birth with congenital anomaly						1	151,274	151,275
Live birth without congenital anomaly						4	342,256	342,260
Unidentified / unknown outcome						0	162,075	162,075

Table 10.M. Pregnancy outcomes by exposure to active controls in congenital anomaly models (Amendment 2 analysis).

B, Before pregnancy; T1, first trimester; T2-T3, after first trimester; D, during all pregnancy; U, unknown; E, all exposed cases; N, non-exposed cases; All, all cases.

Pregnancy outcomes	Timing of carbamazepine_systemic exposure in pregnancy							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy					17	17	10,537	10,554
Spontaneous abortion					320	320	127,836	128,156
Elective termination (no foetal defects or unknown)					1,021	1,021	300,072	301,093
Stillbirth without foetal defects						8	3,368	3,376
Live birth with congenital anomaly	110	168	146	106		228	151,047	151,275
Live birth without congenital anomaly	224	350	328	227		504	341,756	342,260
Unidentified / unknown outcome					1,150	1,150	160,925	162,075

Pregnancy outcomes	Timing of isotretinoin_local exposure in pregnancy							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy						4	10,550	10,554
Spontaneous abortion					102	102	128,054	128,156
Elective termination (no foetal defects or unknown)					268	268	300,825	301,093
Stillbirth without foetal defects						2	3,374	3,376
Live birth with congenital anomaly	54	74	24			142	151,133	151,275
Live birth without congenital anomaly	99	150	55			290	341,970	342,260
Unidentified / unknown outcome					189	189	161,886	162,075

Pregnancy outcomes	Timing of isotretinoin_systemic exposure in pregnancy							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy						4	10,550	10,554
Spontaneous abortion					48	48	128,108	128,156
Elective termination (no foetal defects or unknown)					365	365	300,728	301,093
Stillbirth without foetal defects						1	3,375	3,376
Live birth with congenital anomaly		13				26	151,249	151,275
Live birth without congenital anomaly	30	32	20			72	342,188	342,260
Unidentified / unknown outcome					224	224	161,851	162,075

Pregnancy outcomes	Timing of lithium_systemic exposure in pregnancy							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy						1	10,553	10,554
Spontaneous abortion						9	128,147	128,156
Elective termination (no foetal defects or unknown)					58	58	301,035	301,093
Stillbirth without foetal defects						0	3,376	3,376
Live birth with congenital anomaly						13	151,262	151,275
Live birth without congenital anomaly		10				11	342,249	342,260
Unidentified / unknown outcome					82	82	161,993	162,075

Pregnancy outcomes	Timing of valproic_acid_systemic exposure in pregnancy							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy						8	10,546	10,554
Spontaneous abortion					172	172	127,984	128,156
Elective termination (no foetal defects or unknown)					555	555	300,538	301,093
Stillbirth without foetal defects						8	3,368	3,376
Live birth with congenital anomaly	63	130	146	106		182	151,093	151,275
Live birth without congenital anomaly	147	268	286	205		361	341,899	342,260
Unidentified / unknown outcome					499	499	161,576	162,075

10.3.2. Summary table of pregnancy outcomes (Amendment 1)

Definition of outcome categories and drug exposure periods follow the relevant CHMP recommendations {EMEA/CHMP, 2005 #17}. Summary tables of pregnancy outcomes by exposure to butoconazole, therapeutic controls, or active controls are shown in **Table 10.N – Table 10.Q**.

Table 10.N. Pregnancy outcomes by butoconazole exposure (Amendment 1 analysis).
B, Before pregnancy; T1, first trimester; T2-T3, after first trimester; D, during all pregnancy; U, unknown; E, all exposed cases; N, non-exposed cases; All, all cases.

Pregnancy Outcomes	Timing of butoconazole exposure in pregnancy (Amendment 1 definitions)							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy					52	52	10,502	10,554
Spontaneous abortion					1,109	1,109	126,995	128,104
Elective termination (no foetal defects or unknown)					1,734	1,734	299,224	300,958
Elective termination (foetal defects)						1	186	187
Stillbirth with foetal defects						1	37	38
Stillbirth without foetal defects		14	18			35	3,303	3,338
Live birth with congenital anomaly	729	1,096	3,083	108		4,759	187,369	192,128
Live birth without congenital anomaly	885	1,607	4,875	199		7,074	294,333	301,407
Unidentified / unknown outcome					2,178	2,178	159,897	162,075

Table 10.O. Pregnancy outcomes by exposure to therapeutic controls (Amendment 1 analysis).
B, Before pregnancy; T1, first trimester; T2-T3, after first trimester; D, during all pregnancy; U, unknown; E, all exposed cases; N, non-exposed cases; All, all cases.

Pregnancy Outcomes	Timing of clotrimazole exposure in pregnancy (Amendment 1 definitions)							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy					62	62	10,492	10,554
Spontaneous abortion					2,396	2,396	125,708	128,104
Elective termination (no foetal defects or unknown)					4,079	4,079	296,879	300,958
Elective termination (foetal defects)						10	177	187
Stillbirth with foetal defects						1	37	38
Stillbirth without foetal defects		55	231	18		274	3,064	3,338
Live birth with congenital anomaly	869	4,778	21,924	1,483		25,801	166,327	192,128
Live birth without congenital anomaly	1,223	7,235	33,987	2,334		39,692	261,715	301,407
Unidentified / unknown outcome					4,006	4,006	158,069	162,075

Pregnancy Outcomes	Timing of metronidazole_local exposure in pregnancy (Amendment 1 definitions)							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy					149	149	10,405	10,554
Spontaneous abortion					3,332	3,332	124,772	128,104
Elective termination (no foetal defects or unknown)					8,045	8,045	292,913	300,958
Elective termination (foetal defects)						4	183	187
Stillbirth with foetal defects						3	35	38
Stillbirth without foetal defects	15	52	253			310	3,028	3,338
Live birth with congenital anomaly	1,365	3,128	24,453	770		27,859	164,269	192,128
Live birth without congenital anomaly	2,006	4,732	38,424	1,185		43,540	257,867	301,407
Unidentified / unknown outcome					6,685	6,685	155,390	162,075

Pregnancy Outcomes	Timing of metronidazole_systemic exposure in pregnancy (Amendment 1 definitions)							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy					140	140	10,414	10,554
Spontaneous abortion					1,774	1,774	126,330	128,104
Elective termination (no foetal defects or unknown)					4,963	4,963	295,995	300,958
Elective termination (foetal defects)							185	187
Stillbirth with foetal defects							38	38
Stillbirth without foetal defects		17	35			56	3,282	3,338
Live birth with congenital anomaly	718	905	2,647	56		4,167	187,961	192,128
Live birth without congenital anomaly	1,023	1,313	3,841	68		6,050	295,357	301,407
Unidentified / unknown outcome					3,895	3,895	158,180	162,075

Pregnancy Outcomes	Timing of miconazole_local exposure in pregnancy (Amendment 1 definitions)							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy					142	142	10,412	10,554
Spontaneous abortion					3,175	3,175	124,929	128,104
Elective termination (no foetal defects or unknown)					7,597	7,597	293,361	300,958
Elective termination (foetal defects)							183	187
Stillbirth with foetal defects							35	38
Stillbirth without foetal defects	15	51	239			297	3,041	3,338
Live birth with congenital anomaly	1,321	3,057	23,291	727		26,638	165,490	192,128
Live birth without congenital anomaly	1,942	4,591	36,983	1,123		41,970	259,437	301,407
Unidentified / unknown outcome					6,089	6,089	155,986	162,075

Pregnancy Outcomes	Timing of miconazole_systemic exposure in pregnancy (Amendment 1 definitions)							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy							10,554	10,554
Spontaneous abortion							128,104	128,104
Elective termination (no foetal defects or unknown)							300,958	300,958
Elective termination (foetal defects)							187	187
Stillbirth with foetal defects							38	38
Stillbirth without foetal defects							3,338	3,338
Live birth with congenital anomaly							192,128	192,128
Live birth without congenital anomaly							301,407	301,407
Unidentified / unknown outcome							162,075	162,075

Pregnancy Outcomes	Timing of nystatin_local exposure in pregnancy (Amendment 1 definitions)							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy							10,554	10,554
Spontaneous abortion							128,104	128,104
Elective termination (no foetal defects or unknown)							300,958	300,958
Elective termination (foetal defects)							187	187
Stillbirth with foetal defects							38	38
Stillbirth without foetal defects							3,338	3,338
Live birth with congenital anomaly							192,128	192,128
Live birth without congenital anomaly							301,407	301,407
Unidentified / unknown outcome							162,075	162,075

Pregnancy Outcomes	Timing of nystatin_systemic exposure in pregnancy (Amendment 1 definitions)							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy							10,554	10,554
Spontaneous abortion					15	15	128,089	128,104
Elective termination (no foetal defects or unknown)					23	23	300,935	300,958
Elective termination (foetal defects)							187	187
Stillbirth with foetal defects							38	38
Stillbirth without foetal defects							3,338	3,338
Live birth with congenital anomaly		11	15			30	192,098	192,128
Live birth without congenital anomaly		14	26			47	301,360	301,407
Unidentified / unknown outcome					26	26	162,049	162,075

Table 10.P. Pregnancy outcomes by exposure to active controls in spontaneous abortion models (Amendment 1 analysis).

B, Before pregnancy; T1, first trimester; T2-T3, after first trimester; D, during all pregnancy; U, unknown; E, all exposed cases; N, non-exposed cases; All, all cases.

Pregnancy Outcomes	Timing of celecoxib exposure in pregnancy (Amendment 1 definitions)							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy							10,554	10,554
Spontaneous abortion							128,101	128,104
Elective termination (no foetal defects or unknown)					11	11	300,947	300,958
Elective termination (foetal defects)							187	187
Stillbirth with foetal defects							38	38
Stillbirth without foetal defects							3,338	3,338
Live birth with congenital anomaly							192,119	192,128
Live birth without congenital anomaly							301,400	301,407
Unidentified / unknown outcome					32	32	162,043	162,075

Pregnancy Outcomes	Timing of diclofenac_local exposure in pregnancy (Amendment 1 definitions)							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy					18	18	10,536	10,554
Spontaneous abortion					428	428	127,676	128,104
Elective termination (no foetal defects or unknown)					1,177	1,177	299,781	300,958
Elective termination (foetal defects)							187	187
Stillbirth with foetal defects							38	38
Stillbirth without foetal defects		10				14	3,324	3,338
Live birth with congenital anomaly	132	246	362	43		668	191,460	192,128
Live birth without congenital anomaly	204	420	557	83		1,043	300,364	301,407
Unidentified / unknown outcome					1,564	1,564	160,511	162,075

Pregnancy Outcomes	Timing of diclofenac_systemic exposure in pregnancy (Amendment 1definitions)							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy					406	406	10,148	10,554
Spontaneous abortion					6,138	6,138	121,966	128,104
Elective termination (no foetal defects or unknown)					15,696	15,696	285,262	300,958
Elective termination (foetal defects)							180	187
Stillbirth with foetal defects							36	38
Stillbirth without foetal defects	37	94	48			164	3,174	3,338
Live birth with congenital anomaly	3,384	4,683	2,588	372		9,773	182,355	192,128
Live birth without congenital anomaly	4,958	6,902	4,035	562		14,568	286,839	301,407
Unidentified / unknown outcome					13,341	13,341	148,734	162,075

Pregnancy Outcomes	Timing of ibuprofen_local exposure in pregnancy (Amendment 1 definitions)							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy							10,554	10,554
Spontaneous abortion							128,102	128,104
Elective termination (no foetal defects or unknown)							300,957	300,958
Elective termination (foetal defects)							187	187
Stillbirth with foetal defects							38	38
Stillbirth without foetal defects							3,338	3,338
Live birth with congenital anomaly							192,128	192,128
Live birth without congenital anomaly							301,406	301,407
Unidentified / unknown outcome							162,073	162,075

Pregnancy Outcomes	Timing of ibuprofen_systemic exposure in pregnancy (Amendment 1 definitions)							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy							10,552	10,554
Spontaneous abortion					30	30	128,074	128,104
Elective termination (no foetal defects or unknown)					75	75	300,883	300,958
Elective termination (foetal defects)							187	187
Stillbirth with foetal defects							38	38
Stillbirth without foetal defects							3,337	3,338
Live birth with congenital anomaly	24	31				61	192,067	192,128
Live birth without congenital anomaly	25	41	19			85	301,322	301,407
Unidentified / unknown outcome					61	61	162,014	162,075

Pregnancy Outcomes	Timing of indomethacin_local exposure in pregnancy (Amendment 1 definitions)							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy							10,553	10,554
Spontaneous abortion							128,102	128,104
Elective termination (no foetal defects or unknown)							300,954	300,958
Elective termination (foetal defects)							187	187
Stillbirth with foetal defects							38	38
Stillbirth without foetal defects							3,338	3,338
Live birth with congenital anomaly							192,121	192,128
Live birth without congenital anomaly			11			16	301,391	301,407
Unidentified / unknown outcome							162,068	162,075

Pregnancy Outcomes	Timing of indomethacin_systemic exposure in pregnancy (Amendment 1 definitions)							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy							10,550	10,554
Spontaneous abortion					76	76	128,028	128,104
Elective termination (no foetal defects or unknown)					175	175	300,783	300,958
Elective termination (foetal defects)							187	187
Stillbirth with foetal defects							38	38
Stillbirth without foetal defects							3,336	3,338
Live birth with congenital anomaly	26	43	57			119	192,009	192,128
Live birth without congenital anomaly	46	57	69			167	301,240	301,407
Unidentified / unknown outcome					253	253	161,822	162,075

Pregnancy Outcomes	Timing of naproxen_local exposure in pregnancy (Amendment 1 definitions)							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy							10,554	10,554
Spontaneous abortion							128,104	128,104
Elective termination (no foetal defects or unknown)							300,958	300,958
Elective termination (foetal defects)							187	187
Stillbirth with foetal defects							38	38
Stillbirth without foetal defects							3,338	3,338
Live birth with congenital anomaly							192,128	192,128
Live birth without congenital anomaly							301,407	301,407
Unidentified / unknown outcome							162,075	162,075

Pregnancy Outcomes	Timing of naproxen_systemic exposure in pregnancy (Amendment 1 definitions)							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy					158	158	10,396	10,554
Spontaneous abortion					1,241	1,241	126,863	128,104
Elective termination (no foetal defects or unknown)					2,830	2,830	298,128	300,958
Elective termination (foetal defects)							186	187
Stillbirth with foetal defects							37	38
Stillbirth without foetal defects		15				26	3,312	3,338
Live birth with congenital anomaly	554	734	240	40		1,431	190,697	192,128
Live birth without congenital anomaly	772	1,009	362	62		2,002	299,405	301,407
Unidentified / unknown outcome					3,707	3,707	158,368	162,075

Pregnancy Outcomes	Timing of rofecoxib exposure in pregnancy (Amendment 1 definitions)							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy							10,554	10,554
Spontaneous abortion							128,104	128,104
Elective termination (no foetal defects or unknown)							300,956	300,958
Elective termination (foetal defects)							187	187
Stillbirth with foetal defects							38	38
Stillbirth without foetal defects							3,338	3,338
Live birth with congenital anomaly							192,127	192,128
Live birth without congenital anomaly							301,403	301,407
Unidentified / unknown outcome							162,075	162,075

Table 10.Q. Pregnancy outcomes by exposure to active controls in congenital anomaly models (Amendment 1 analysis).

B, Before pregnancy; T1, first trimester; T2-T3, after first trimester; D, during all pregnancy; U, unknown; E, all exposed cases; N, non-exposed cases; All, all cases.

Pregnancy Outcomes	Timing of carbamazepine_systemic exposure in pregnancy (Amendment 1 definitions)							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy					17	17	10,537	10,554
Spontaneous abortion					320	320	127,784	128,104
Elective termination (no foetal defects or unknown)					1,021	1,021	299,937	300,958
Elective termination (foetal defects)							187	187
Stillbirth with foetal defects							38	38
Stillbirth without foetal defects							3,330	3,338
Live birth with congenital anomaly	144	217	195	140		298	191,830	192,128
Live birth without congenital anomaly	190	301	279	193		434	300,973	301,407
Unidentified / unknown outcome					1,150	1,150	160,925	162,075

Pregnancy Outcomes	Timing of isotretinoin_local exposure in pregnancy (Amendment 1 definitions)							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy							10,550	10,554
Spontaneous abortion					102	102	128,002	128,104
Elective termination (no foetal defects or unknown)					268	268	300,690	300,958
Elective termination (foetal defects)							187	187
Stillbirth with foetal defects							38	38
Stillbirth without foetal defects							3,336	3,338
Live birth with congenital anomaly	73	94	32			189	191,939	192,128
Live birth without congenital anomaly	80	130	47			243	301,164	301,407
Unidentified / unknown outcome					189	189	161,886	162,075

Pregnancy Outcomes	Timing of isotretinoin_systemic exposure in pregnancy (Amendment 1 definitions)							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy					4	4	10,550	10,554
Spontaneous abortion					48	48	128,056	128,104
Elective termination (no foetal defects or unknown)					365	365	300,593	300,958
Elective termination (foetal defects)							187	187
Stillbirth with foetal defects							38	38
Stillbirth without foetal defects						1	3,337	3,338
Live birth with congenital anomaly	10	16	10			30	192,098	192,128
Live birth without congenital anomaly	28	29	19			68	301,339	301,407
Unidentified / unknown outcome					224	224	161,851	162,075

Pregnancy Outcomes	Timing of lithium_systemic exposure in pregnancy (Amendment 1 definitions)							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy							10,553	10,554
Spontaneous abortion							128,095	128,104
Elective termination (no foetal defects or unknown)					58	58	300,900	300,958
Elective termination (foetal defects)							187	187
Stillbirth with foetal defects							38	38
Stillbirth without foetal defects							3,338	3,338
Live birth with congenital anomaly						13	192,115	192,128
Live birth without congenital anomaly		10				11	301,396	301,407
Unidentified / unknown outcome					82	82	161,993	162,075

Pregnancy Outcomes	Timing of valproic_acid_systemic exposure in pregnancy (Amendment 1 definitions)							
	B	T1	T2-T3	D	U	E	N	All
Ectopic pregnancy							10,546	10,554
Spontaneous abortion					171	171	127,933	128,104
Elective termination (no foetal defects or unknown)					554	554	300,404	300,958
Elective termination (foetal defects)							185	187
Stillbirth with foetal defects							38	38
Stillbirth without foetal defects							3,330	3,338
Live birth with congenital anomaly	79	159	178	129		221	191,907	192,128
Live birth without congenital anomaly	131	240	254	182		322	301,085	301,407
Unidentified / unknown outcome					499	499	161,576	162,075

Note that missing numbers in the above tables can refer to any value between 0 and 9, as the OEP database does not provide analysis results in patient groups below N=10. However, the difference between the number of not exposed cases and all cases (the “N” and “All” columns) give a hint on the exact value of exposed cases (column E) for all rows of Tables 10.4.2.A-D. Accordingly, no pregnancy was exposed to systemic miconazole, local nystatin, or local naproxen. Considering local ibuprophen, all together 6 pregnancies were exposed: 2 spontaneous abortions, 1 elective termination without foetal defects, 1 live birth without congenital anomaly, and 2 pregnancies with unidentified / unknown outcome. Considering rofecoxib, all together 7 pregnancies were exposed: 2 elective terminations without foetal defects, 1 live birth with congenital anomaly, and 4 live births without congenital anomaly.

10.3.3. Rate of congenital anomalies / foetal malformations in Amendment 1 analyses

According to the applied criteria of Protocol Amendment 1, about ~40% of the evaluated births were classified as congenital anomaly cases (irrespective of drug exposure) in all analyses not restricted to certain code subgroups as shown in Table 10.3.3.A. This rate is about ten times higher than the previously published 3-5% malformation rates in Hungary {Acs, 2010 #4}{National_Institute_for_Health_Development, 2013 #43}. This strong dilution of true cases by false positive records would prevent the detection of drug-related teratogenicity risk signals, therefore it was decided to restrict the criteria for the identification of malformations in Protocol Amendment 2. The restriction of malformation definitions was approached in three ways: a) exclusion of mild anomalies from all analyses; b) exclusion of outpatient reports in sensitivity analyses; and c) analyses by code subgroups. For details, please see Protocol Amendment 2, ANNEX 3.1.4. Expected and observed rates of cases with congenital anomaly code subgroups in Amendment 2 analyses are shown in Sections 10.4.2.1-10.4.2.35.

Table 10.R. Observed rate of congenital anomalies in Amendment 1 analyses.
CA, congenital anomaly; FD, foetal defect; LB, live birth; M, main analysis; S, sensitivity analysis.

Analysis	Definition of Cases	Definition of Controls	Cases / (Cases + Controls)
M	Elective termination with FD, Stillbirth with FD, Live birth with CA	Live birth without CA	38.96%
S1			
S2			
S3		live births without CA, stillbirths without FD	38.70%
S4	Elective termination with FD, Stillbirth with FD, Live birth with CA; AFP report in 26 weeks before outcome.	Live birth without CA; AFP report in 26 weeks before outcome.	39.26%
S5	Stillbirth with FD, Live birth with CA.	Live birth without CA	38.93%
S6	Elective termination with FD, Stillbirth with FD, Live birth with CA; restricted to cases with any anomaly indicative of cleft lip/palate (see details in Section 10.4.2).		0.17%
S7	Elective termination with FD, Stillbirth with FD, Live birth with CA; restricted to cases with any anomaly indicative of abdominal wall defects (see details in Section 10.4.2).		0.09%
S8	Live birth in 2005, with FD / CA reported until the end of 2012.	Live birth in 2005, with FD / CA not reported until the end of 2012.	48.09%

S9	Elective termination with FD, Stillbirth with FD, Live birth with CA; cases fulfilling the criteria of any alternative estimation of Day1 of pregnancy are excluded.	Live birth without CA; controls fulfilling the criteria of any alternative estimation of Day1 of pregnancy are excluded.	38.94%

10.4. Main results

This was the first study with the intention to determine pregnancy outcomes, pregnancy periods, drug exposure, pregnancy risks and confounding factors solely from the OEP database. In this pioneering exercise, the original study protocol failed to identify most mother – offspring pairs, since it did not match the transient and permanent social security numbers of the investigated children, resulting in the loss of medical follow-up of about 440 000 live births. Moreover, the exact hierarchy of rules for redundant and conflicting pregnancy outcome codes has not been defined in the original protocol, making pregnancy outcomes ambiguous in cases with multiple outcome records. Accordingly, as justified in Protocol Amendment 2, the study has not been analysed as planned in the original protocol. Instead, all descriptive statistics and statistical analyses (including the sensitivity analyses) are conducted according to Protocol Amendment 2 and Protocol Amendment 1.

10.4.1. Logistic regression models on spontaneous abortions

10.4.1.1. Co-primary analyses on SA risk

In Protocol Amendment 1, altered risk of spontaneous abortion is inferred if the 95% confidence interval of the adjusted odds ratio of spontaneous abortion in pregnancies exposed to butoconazole (vs. not exposed pregnancies) does not include the value 1.00 in the main analysis of spontaneous abortion risk. In this analysis, the „adjusted(2)" odds ratios were considered, i.e. odds ratios adjusted for maternal age, local miconazole / systemic miconazole / clotrimazole / local nystatin / systemic nystatin / local metronidazole / systemic metronidazole and/or local diclofenac / systemic diclofenac / local naproxen / systemic naproxen / celecoxib / local ibuprofen / systemic ibuprofen / rofecoxib / local indomethacin / systemic indomethacin 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). In Amendment 1 analyses, all drug exposure parameters were binary (yes / no).

In the Amendment 2 co-primary analysis of SA risk, all drug exposure parameters were continuous variables expressed in days of therapy (DOTs). Alternatively, in a post-hoc analysis, exposure to gynecology anti-infective drugs was expressed in number of cures (since treatment duration is heterogenous across gynecology anti-infective drugs). In all Amendment 2 analyses, the propensity score also included the socioeconomic status of the maternal residence at micro-region level, and urban/rural status, beyond the Amendment 1 defined variables.

Results of the co-primary analyses on SA risk are summarized in **Table 10.S**.

Table 10.S. Results of the co-primary analyses on SA risk of butoconazole.

Analysis	Drug exposure unit	„Adjusted(2)" OR (95%CI) for butoconazole in the main analysis
Amendment 1 co-primary	Binary	1.0517 (0.9825 – 1.1259)
Amendment 2 co-primary	Continuous (all in DOTs)	1.0493 (0.9833 – 1.1198)
Amendment 2 post hoc	Continuous (active controls in DOTs; gynecology anti-infectives in number of cures)	1.0511 (0.9893 – 1.1168)

These analyses did not provide evidence for butoconazole exposure to increase the risk of SA.

10.4.1.2. Sensitivity analyses of butoconazole and therapeutic controls

Odds Ratios for the investigated gynecology anti-infective drugs as adjusted to all investigated confounders are shown in **Figure 10.K** and **Figure 10.L** for Amendment 2 and Amendment 1 analyses, respectively. For all spontaneous abortion risk results in tabular format, please see Section 15.2. For discussion of findings, please see Section 11.1.1.

Figure 10.K. Odds Ratios for spontaneous abortion by gynecology anti-infective drug exposure: Amendment 2 results.

Upper panel: gynecology drug exposure unit = number of cures; Bottom panel: gynecology drug exposure unit = days of therapy (DOTs). The unit of exposure to active controls was DOT in both panels. Analysis version codes M and S1 – S6 stand for the main analysis and sensitivity analyses 1 to 6, respectively. BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatin; OR, odds ratio; syst, systemic administration.

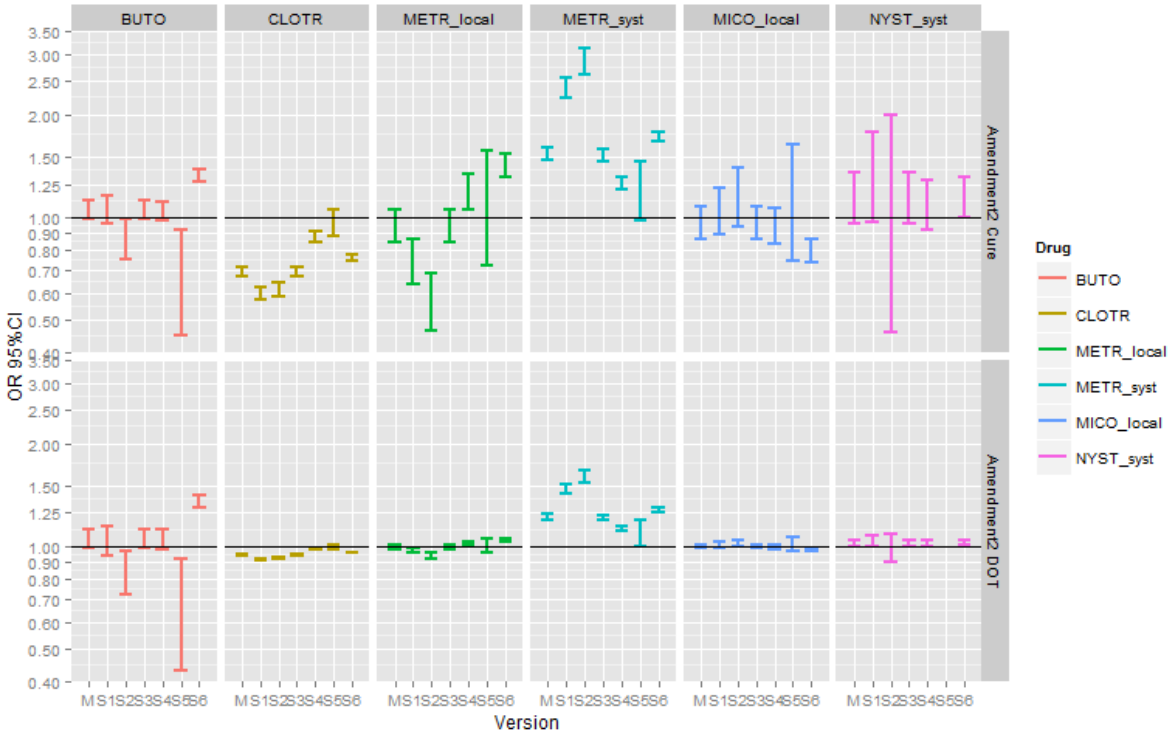
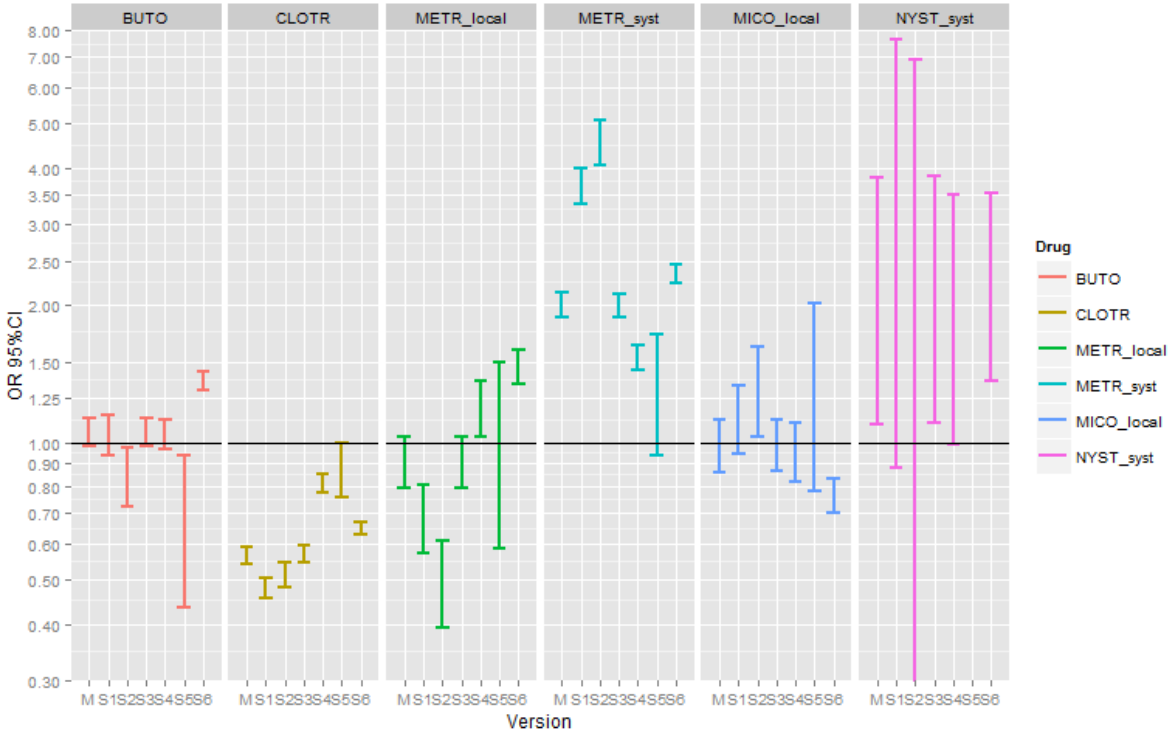


Figure 10.L. Odds Ratios for spontaneous abortion by gynecology anti-infective drug exposure: Amendment 1 results.

All drug exposure parameters were binary (yes / no). Analysis version codes M and S1 – S6 stand for the main analysis and sensitivity analyses 1 to 6, respectively. BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatin; OR, odds ratio; syst, systemic administration.



10.4.1.3. Active controls and SA risk

Odds Ratios for the investigated active control drugs as adjusted to all investigated confounders are shown in **Figure 10.M** and **Figure 10.N** for Amendment 2 and Amendment 1 analyses, respectively. For all spontaneous abortion risk results in tabular format, please see Section 15.2. For discussion of findings, please see Section 11.1.1.

Figure 10.M. Odds Ratios for spontaneous abortion by exposure to active controls: Amendment 2 results, adjusted to all measured confounders.

Upper panel: gynecology drug exposure unit = number of cures; Bottom panel: gynecology drug exposure unit = days of therapy (DOTs). The unit of exposure to active controls was DOT in both panels. Analysis version codes M and S1 – S6 stand for the main analysis and sensitivity analyses 1 to 6, respectively. CELECXB, celecoxib; DICLOF, diclofenac; IBUPR, ibuprofen; INDOM, indomethacin; NAPR, naproxen; OR, odds ratio; syst, systemic administration.

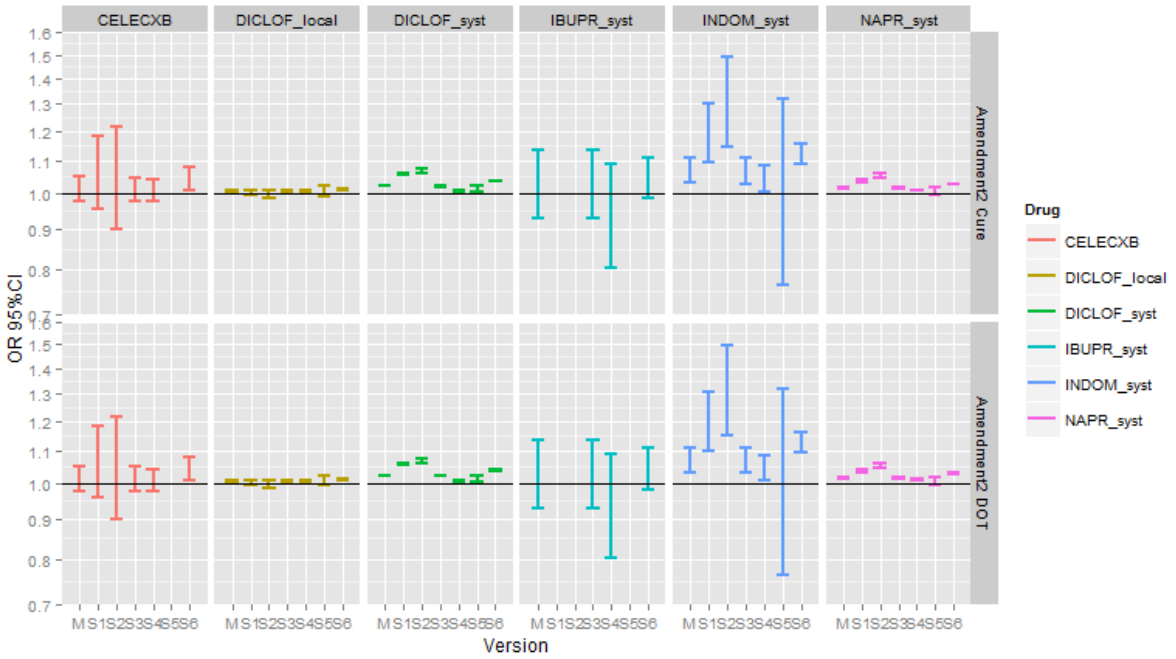
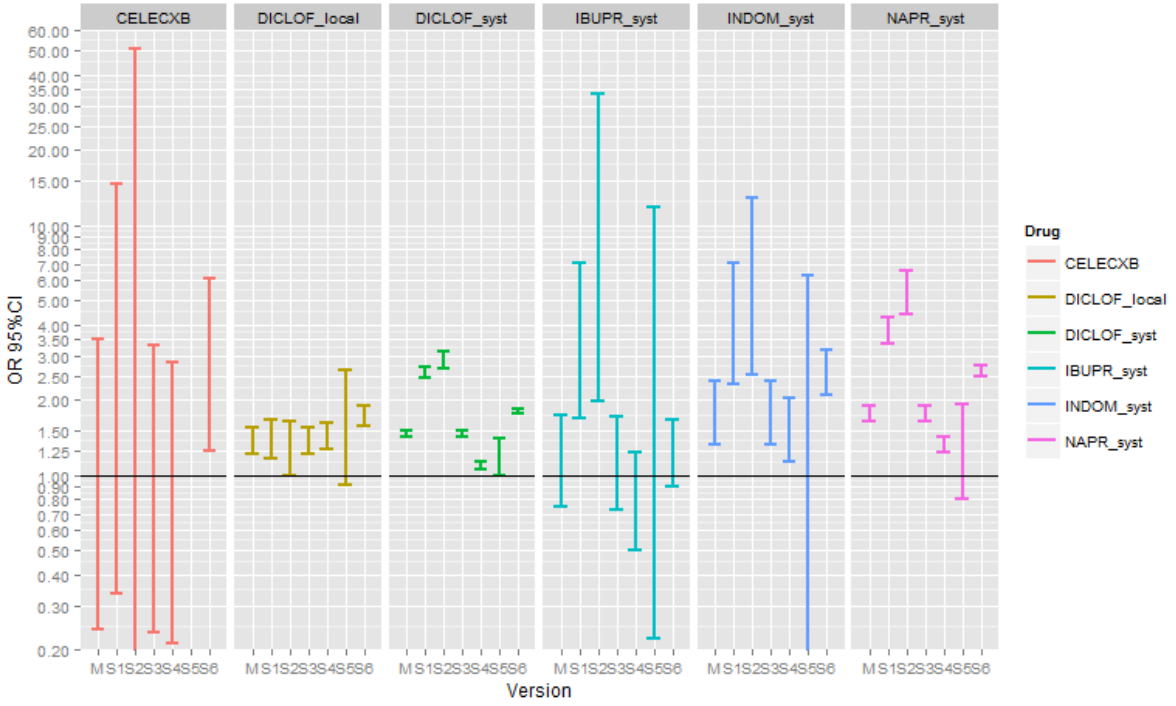


Figure 10.N. Odds Ratios for spontaneous abortion by exposure to active controls: Amendment 1 results, adjusted to all measured confounders.

All drug exposure parameters were binary (yes / no). Analysis version codes M and S1 – S6 stand for the main analysis and sensitivity analyses 1 to 6, respectively. CELECXB, celecoxib; DICLOF, diclofenac; IBUPR, ibuprofen; INDOM, indomethacin; NAPR, naproxen; OR, odds ratio; syst, systemic administration.



10.4.1.4. Maternal age and SA risk

Odds Ratios for maternal age groups as adjusted to all investigated confounders are shown in **Figure 10.O** and **Figure 10.P** for Amendment 2 and Amendment 1 analyses, respectively. For all spontaneous abortion risk results in tabular format, please see Section 15.2. For discussion of findings, please see Section 11.1.1.

Figure 10.O. Odds Ratios for spontaneous abortion by maternal age: Amendment 2 results adjusted to all measured confounders.
Upper panel: gynecology drug exposure unit = number of cures; Bottom panel: gynecology drug exposure unit = days of therapy (DOTs). The unit of exposure to active controls was DOT in both panels. Analysis version codes M and S1 – S6 stand for the main analysis and sensitivity analyses 1 to 6, respectively. Horizontal facets by maternal age in years, reference age group: 25-29 years.

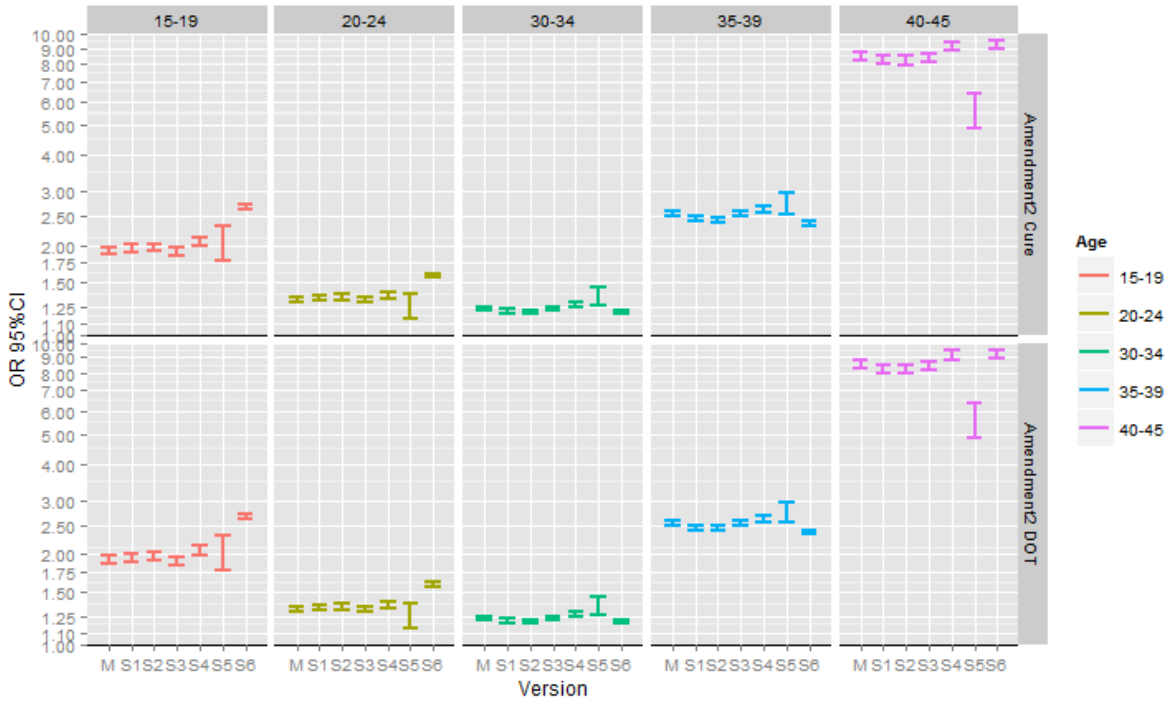
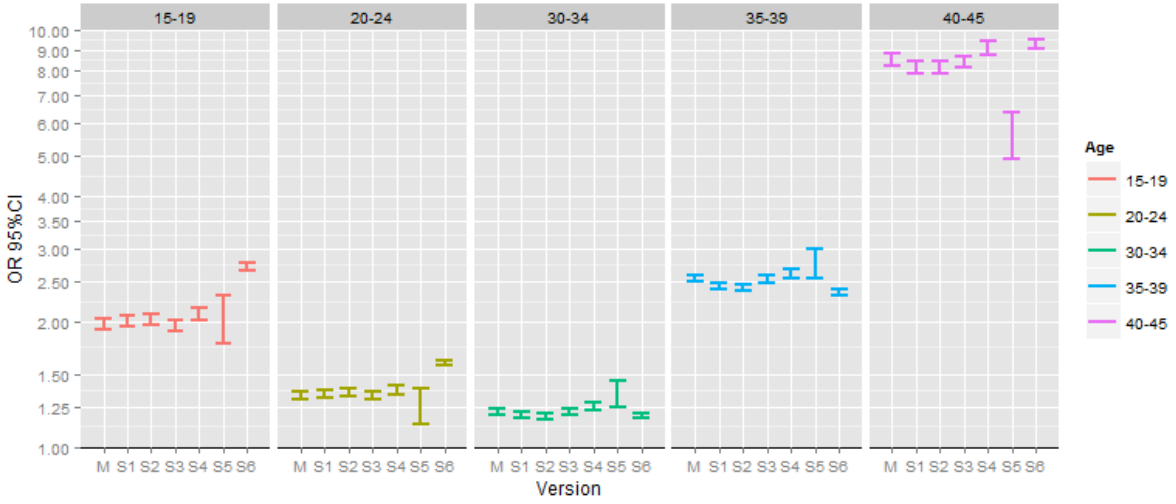


Figure 10.P. Odds Ratios for spontaneous abortion by maternal age: Amendment 1 results, adjusted to all measured confounders.
All drug exposure parameters were binary (yes / no). Analysis version codes M and S1 – S6 stand for the main analysis and sensitivity analyses 1 to 6, respectively. Horizontal facets by maternal age in years, reference age group: 25-29 years.



10.4.2. Logistic regression model on congenital anomalies

10.4.2.1. Co-primary analyses on CA risk

In Protocol Amendment 1, altered risk of congenital anomalies is inferred if the 95% confidence interval of the adjusted odds ratio of foetal defect/congenital abnormality in pregnancies exposed to butoconazole in the first trimester (vs. not exposed pregnancies) does not include the value 1.00 in the main analysis of teratogenicity risk. In this analysis, the „adjusted(2)" odds ratios were considered, i.e. odds ratios adjusted for maternal age, local miconazole / systemic miconazole / clotrimazole / local nystatin /systemic nystatin / local metronidazole / systemic metronidazole and/or systemic carbamazepine / systemic isotretinoin / local isotretionin / systemic lithium / systemic valproic acid 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, calendar effect (year and month). In Amendment 1 analyses, all drug exposure parameters were binary (yes / no). Due to the unexpectedly high number of congenital anomaly cases, Amendment 1 co-primary analysis of congenital anomaly risk is considered to be not relevant (of every 10 identified pregnancies with congenital anomaly, roughly 9 were most probably false positive cases in the Amendment 1 main analysis).

In Amendment 2 co-primary analyses, the relevant co-primary endpoint refers to the "al1" EUROCAT definition of congenital anomalies, and the propensity score also includes the socioeconomic status of the maternal residence at micro-region level, and urban /rural status, beyond the previously included variables. In the Amendment 2 co-primary analysis of CA risk, all drug exposure parameters were continuous variables expressed in days of therapy (DOTs). Alternatively, in a post-hoc analysis, exposure to gynecology anti-infective drugs was expressed in number of cures (since treatment duration was heterogenous across gynecology anti-infective drugs, and the risk associated to one treatment cure is clinically more relevant than the risk associated to one day of therapy). Due to the unexpectedly high number of congenital anomaly cases, the main Amendment 2 co-primary analysis of congenital anomaly risk is considered to be not relevant (of 10 identified pregnancies with congenital anomaly, roughly 8 were most probably false positive cases in the Amendment 2 main analysis: see Section 15.3.35). However, in sensitivity analyses S6-S8 where only inpatient records were analysed, the overall rate of „al1" anomalies was very similar to the rate observed in the Hungarian Congenital Anomaly Registry (55.34 per 1,000 live births in our study, and 53.1 per 1,000 live births in the registry). Of these, S7 sensitivity analyses are of outmost relevance since the estimation of first day of pregnancy was identical to that in the main analysis, and this estimate was confirmed by descriptive analyses (see Section 10.2.1).

Results of the co-primary analyses and most relevant secondary / post hoc analyses on CA risk are summarized in **Table 10.T**.

Table 10.T. Results of co-primary analyses and most relevant secondary / post hoc analyses on the congenital anomaly risk associated to first trimester butoconazole exposure.

Analysis	Drug exposure unit	„Adjusted(2)" OR (95%CI) for first trimester butoconazole exposure	Comment
Amendment 1, co-primary main analysis	Binary	1.0602 (0.9816 – 1.1452)	Not relevant (high rate of false positive cases)
Amendment 2, co-primary main analysis	Continuous (all in DOTs)	1.0063 (0.9324 – 1.0859)	
Amendment 2, post hoc change in main analysis (gynecology exposure in cure numbers)	Continuous (active controls in DOTs; gynecology drugs in number of cures)	1.0059 (0.9322 – 1.0856)	
Amendment 2, most relevant pre-planned secondary analysis (al1 S7)	Continuous (all in DOTs)	0.9715 (0.8318 – 1.1347)	No increased risk with butoconazole
Amendment 2, most relevant post-hoc sensitivity analysis (al1 S7, gynecology exposure in cure numbers)	Continuous (active controls in DOTs; gynecology drugs in number of cures)	0.9729 (0.8331 – 1.1363)	

These analyses did not provide evidence for butoconazole exposure to increase the risk of congenital anomalies in general.

10.4.2.2. Human data on preclinical safety signals of butoconazole

In preclinical safety studies, 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). However, 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, 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).

In our study, dedicated case-control analyses were focusing on the risk of cleft lip/palate and abdominal wall defects in human pregnancies. Main results of these analyses are summarized in Sections 10.4.2.2.1. and 10.4.2.2.2.

10.4.2.2.1. Case-control analyses on cleft lip/palate

Main results of dedicated analyses on the risk of cleft lip/palate associated to butoconazole exposure in human pregnancy are summarized in **Table 10.U.** The results are mixed, three analyses suggest an increased risk of cleft lip/palate while several others (with adequate statistical power) do not.

Table 10.U. Cleft lip/palate associated to butoconazole exposure in human pregnancy.
Crude and not fully adjusted odds ratios, and results for second or third trimester exposure are not included. Sensitivity analyses with irrelevant number of cases are omitted (see Section 9.1.2.3.3 and Section 15.3.11 for details and justification). GYN, gynecology anti-infective drugs; M1, M2, and M3, first, second, and third month of pregnancy; M23, second and third month of pregnancy; T1, first trimester; S(index), sensitivity analysis (index number). Note that less than 10 cases were exposed to butoconazole in the first trimester.

Analysis	Statistically significant findings (OR 95%CI not including 1)	Comment
Amendment 1, sensitivity analysis 6	none	none
Amendment 2, al101 definition, GYN expsoure in DOTs	T1S3: 1.8750 (1.0245 – 3.4313) T1S7: 1.8074 (1.0115 – 3.2296) M23S3: 2.1196 (1.0565 – 4.2526)	42 relevant models with non-significant results, 16 powered for OR 1.1 and 26 powered for OR 1.25 (power at least 80%)
Amendment 2, al101 definition, GYN expsoure in treatment cures	T1S3: 1.8757 (1.0250 – 3.4325) T1S7: 1.8076 (1.0118 – 3.2295) M23S3: 2.1211 (1.0571 – 4.2558)	42 relevant models with non-significant results, 19 powered for OR 1.1 and 23 powered for OR 1.25 (power at least 80%)

10.4.2.2.2. Case-control analyses on abdominal wall defects

Main results of dedicated analyses on the risk of abdominal wall defects associated with butoconazole exposure in human pregnancy are summarized in Table 10.V. The results are mixed, two analyses on exposure in the third month suggest an increased risk of abdominal wall defects while several others (with adequate statistical power) do not.

Table 10.V. Abdominal wall defects associated to butoconazole exposure in human pregnancy. *Crude and not fully adjusted odds ratios, and results for second or third trimester exposure are not included. Sensitivity analyses with irrelevant number of cases are omitted (see Section 9.1.2.3.3, Section 15.3.15, and Section 15.3.16 for details and justification). GYN, gynecology anti-infective drugs; M1, M2, and M3, first, second, and third month of pregnancy; M23, second and third month of pregnancy; T1, first trimester; S(index), sensitivity analysis (index number). Note that less than 10 cases were exposed to butoconazole in the first trimester.*

Analysis	Statistically significant findings (OR 95%CI not including 1)	Comment
Amendment 1, sensitivity analysis 7	none	none
Amendment 2, al49 definition, GYN expsoure in DOTs	none	30 relevant models with non-significant results, 29 powered for OR 1.25 (power at least 80%).
Amendment 2, RG04 definition, GYN expsoure in DOTs	M3S6: 2.4829 (1.1245 – 5.4821)	11 relevant models with non-significant results, all powered for OR 1.1 (power at least 80%)
Amendment 2, al49 definition, GYN expsoure in treatment cures	none	30 relevant models with non-significant results, all powered for OR 1.25 (power at least 80%).
Amendment 2, RG04 definition, GYN expsoure in treatment cures	M3S6: 2.4930 (1.1302 – 5.4991)	11 relevant models with non-significant results, all powered for OR 1.1 (power at least 80%)

10.4.2.3. Risk associated to therapeutic and active controls in Amendment 2 CA models

All of the investigated drugs showed statistically significant increase in the risk of some congenital anomalies – which is not surprising if we consider the chances for false positive signals due to the high number of models. However, by chance, a similar number of significant findings for increased and reduced risk would be expected, which was not the case for any investigated drug in our study. Table 10.W summarizes the number of statistically significant changes in congenital anomaly risk by the direction of change (increased or reduced risk), for the various gynecology anti-infective and active control drugs (all exposure in DOTs). It is apparent that findings of decreased risk are outnumbered by findings of increased risk when gynecology anti-infective drugs are considered. Moreover, for active controls, all significant fiindings indicated increased risk associated with drug exposure. Similar results were found when gynecology drug exposure was captured in the number of treatment cures (not shown). Note that only sensitivity analyses with relevant number of cases are included, as discussed in Section 9.1.2.3.3.

Table 10.W. Statistically significant changes in CA risk, by direction of change and by exposure to drugs (all drug exposures in DOTs).
Crude and not fully adjusted odds ratios, and results for second or third trimester exposure are not included. Sensitivity analyses with irrelevant number of cases are omitted (see Section 9.1.2.3.3 for details and justification).

Drug	Congenital anomaly code groups (No. of models) where drug exposure was a significant …		Ratio of code groups and models where drug exposure was a risk factor / a protective factor
	… risk factor	… protective factor	
Gynecology anti-infective drugs			
butoconazole	al2 (2), al10 (6), al40 (5), al58 (2), al59 (2), al66 (2), al101 (3), RG03 (19), RG04 (1)	al1 (2), al52 (1), al58 (1), al61 (2), al67 (1), RG12 (1)	CA code groups: 9 with significant risk / 6 with significant protection. Models: 42 with significant risk / 8 with significant protection.
clotrimazole	al1 (5), al2 (1), al10 (4), al49 (3), al52 (2), al58 (16), al59 (4), al67 (4), Q383 (5), Q639 (9), Q649 (2), RG11 (8), RG12 (1)	al17 (3), al22 (2), RG13 (5)	CA code groups: 13 with significant risk / 3 with significant protection. Models: 64 with significant risk / 10 with significant protection.
metronidazole (local)	al1 (5), al17 (2), al22 (1), al40 (2), al55 (3), al58 (2), al59 (2), al61 (8), al97 (6), Q383 (2), RG01 (4), RG10 (1), RG11 (1), RG12 (6), RG13 (5)	al10 (1), al34 (2), al58 (1), al59 (1), al97 (4), Q623 (2), RG01 (1), RG10 (2), RG14 (1)	CA code groups: 15 with significant risk / 9 with significant protection. Models: 50 with significant risk / 15 with significant protection.
metronidazole (systemic)	al1 (5), al15 (2), al21 (4), al81 (16),	-	CA code groups: 8 with significant risk / 0 with significant protection.

	al97 (6), Q383 (3), Q623 (3), Q639 (1)		Models: 40 with significant risk / 0 with significant protection.
miconazole (local)	al10 (4), al34 (7), al58 (3), al59 (3), al97 (4), Q638 (5), RG01 (1), RG10 (2), RG14 (1)	al1 (1), al58 (1), al61 (5), al97 (4), RG01 (5), RG03 (2), RG10 (1), RG13 (10)	CA code groups: 9 with significant risk / 8 with significant protection. Models: 30 with significant risk / 29 with significant protection.
nystatin (systemic)	al1 (14), al17 (8), al21 (8), al22 (7), al40 (16), RG03 (24)	-	CA code groups: 6 with significant risk / 0 with significant protection. Models: 77 with significant risk / 0 with significant protection.
Active controls			
carbamazepine	al1 (4), al17 (2), al34 (2), al55 (3), al58 (4), al59 (10), Q623 (2), Q638 (4), RG01 (1), RG03 (16), RG10 (5), RG13 (2)	-	CA code groups: 12 with significant risk / 0 with significant protection. Models: 55 with significant risk / 0 with significant protection.
isotretinoin (local)	al40 (2), al66 (1), Q383 (2), RG03 (3), RG10 (8)	-	CA code groups: 5 with significant risk / 0 with significant protection. Models: 16 with significant risk / 0 with significant protection.
isotretinoin (systemic)	al2 (10), al15 (28), al21 (1)	-	CA code groups: 3 with significant risk / 0 with significant protection. Models: 39 with significant risk / 0 with significant protection.
lithium	-	-	-
valproic acid	al1 (25), al2 (6), al17 (13), al21 (3), al22 (9), al34 (10), al49 (9), al59 (4), RG12 (4), RG14 (7)	-	CA code groups: 10 with significant risk / 0 with significant protection. Models: 90 with significant risk / 0 with significant protection.

The above comparisons suggest that all investigated gynecology anti-infective drugs were associated with significant increase in the rate of some congenitaly anomalies in our study, in a higher extent than expected by chance; and it was particularly the case for active controls where no any protective effect but several signals of increased risk were found (except for lithium, probably due to low number of exposed pregnancies). The identified positive signals are heterogeneous across gynecology anti-infective drugs, which could allow their safety ranking in terms of the associated risk of congenital anomalies. However, the number of anomaly definitions or the number of regression models with positive findings alone is not a relevant basis for this purpose, for the following reasons: 1) the different congenital anomaly definitions reflect different

disease groups of various severity (e.g. severe congenital heart defects, versus congenital anomaly of the tongue; 2) a statistically significant signal may reflect a numerically small or large increase in the odds ratio, with high or low uncertainty; and 3) the baseline odds (what is multiplied by the odds ratio in the exposed population) is highly heterogenous across the various anomalies.

Therefore, to allow more relevant comparisons across gynecology drugs, we calculated the 95% CI range for the expected number of extra congenital anomaly cases in a hypothetical cohort of 10,000 women with first trimester exposure to one treatment cure (for gynecology anti-infectives) or for a 28-day treatment (for active controls), for all anomaly definitions separately (**Figures 10.Q. and 10.R**). Only statistically significant results from the fully adjusted "adjusted(2)" models from sensitivity analyses with relevant number of cases were used for this experiment, and all models for exposure after the first trimester were omitted (drug exposure after organogenesis is most probably not relevant). In models where the exposition window was shorter than 3 month, a proportional fraction of the 10,000 hypopthetical women were considered to be exposed (i.e. in models of second month exposure, only 3,333 women were considered to be exposed, in contrast to models where the exposition window covered the full first trimester). Tabular results for this hypothetical cohort are provided in **Table 10.X**.

Figure 10.Q. Number of extra anomaly cases in 10,000 hypothetical women with first trimester exposure to 1 treatment cure (various duration).
Triangles, point estimates of statistically significant findings; lines, 95% confidence interval of statistically significant findings. BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatin.

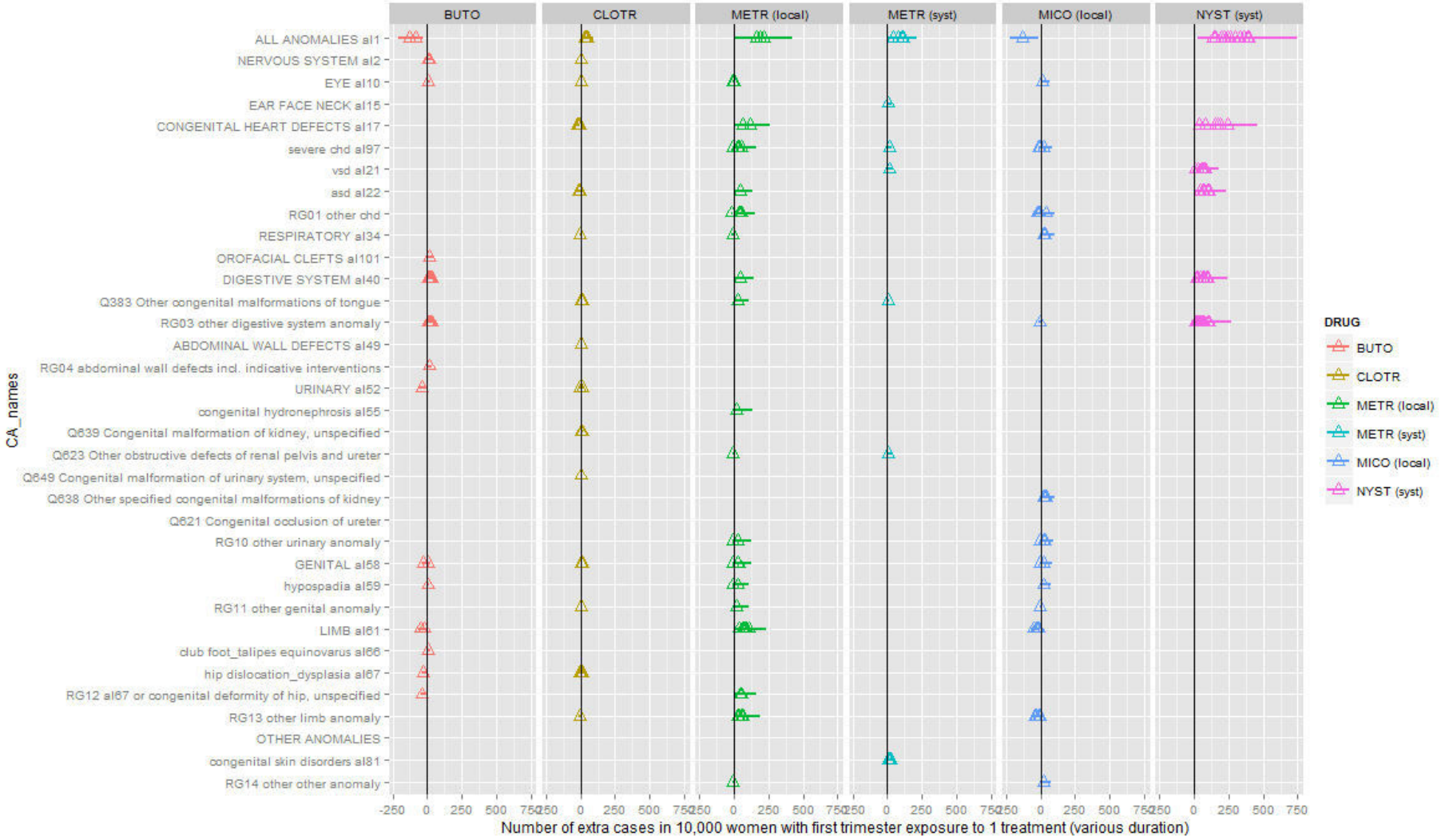


Figure 10.R. Number of extra anomaly cases in 10,000 hypothetical women with first trimester exposure to a 28-day treatment.
Triangles, point estimates of statistically significant findings; lines, 95% confidence interval of statistically significant findings. All exposures in DOTs. CARB, carbamazepine;ISOTR, isotretinoin; syst, systemic; VALPR, valproic acid.

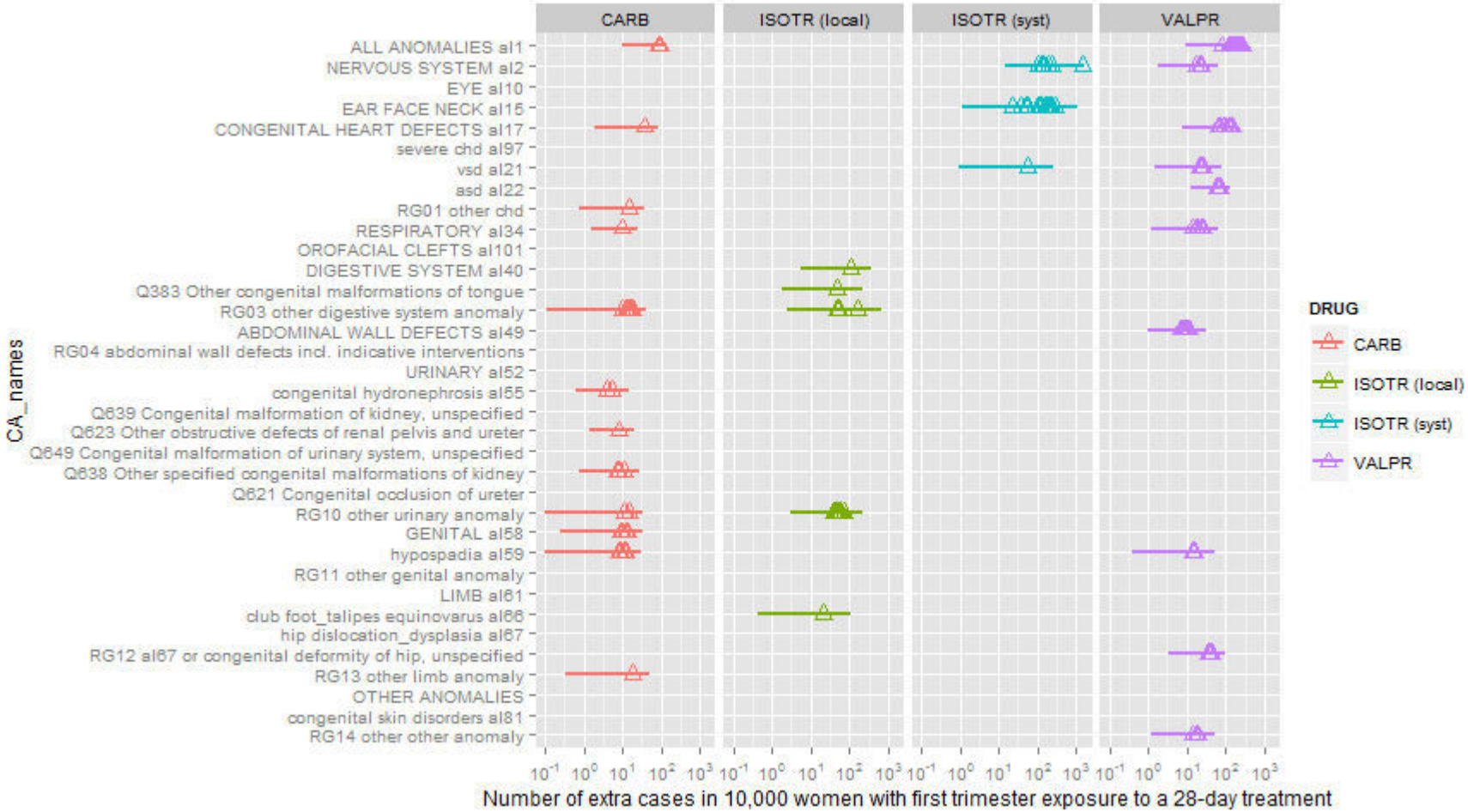


Table 10.X. Point estimates for expected additional congenital anomaly cases in a hypothetical cohort of 10,000 pregnant women exposed in the first trimester to a single treatment course of gynecology anti-infectives or to 28-day treatment with active control drugs.

Range of point estimates (with the number of models with significant findings). Only results from models with relevant case numbers and statistically significant findings are included. Significant findings from 5 or more models are typed in bold. Extra cases and prevented cases are highlighted in red and green, respectively. Gynecology drug exposure is expressed in cure numbers in all of these analyses.

GYNECOLOGY ANTI-INFECTIVE DRUGS	
Butoconazole (1 treatment course)	
other digestive system anomaly (RG03)	**9 to 33 extra cases (19 models)**
digestive system (al40)	**10 to 31 extra cases (5 models)**
eye anomaly (al10)	**4 to 7 extra cases (7 models)**
orofacial clefts (al101)	12 to 14 extra cases (3 models)
abdominal wall defects incl. interventions (RG04)	12 extra cases (1 model)
club foot – talipes equinovarus (al66)	10 extra cases (2 models)
nervous system (al2)	6 to 16 extra cases (2 models)
hypospadia (al59)	7 extra cases (2 models)
genital (al58)	9 extra cases (2 models) or 29 prevented cases (1 model)
all anomalies (al1)	87 to 127 prevented cases (2 models)
urinary (al52)	40 prevented cases (1 model)
al67 or "congenital deformity of hip, unspecified" (RG12)	35 prevented cases (1 model)
limb (al61)	17 to 44 prevented cases (2 models)
hip dislocation or dysplasia (al67)	26 prevented cases (1 model)
Clotrimazole (1 treatment course)	
all anomalies (al1)	**27 to 51 extra cases (5 models)**
congenital malformation of kidney, unspecified (Q639)	**4 to 14 extra cases (8 models)**
other congenital malformations of tongue (Q383)	**3 to 9 extra cases (7 models)**
genital (al58)	**3 to 8 extra cases (13 models)**
other genital anomaly (RG11)	**2 to 4 extra cases; 10 models)**
urinary (al52)	15 extra cases (2 models) or 6.7 prevented cases (1 model)
congenital malformation of urinary system, unspecified (Q649)	6 extra cases (2 models)
hip dislocation or dysplasia (al67)	6 to 9 extra cases (4 models) or 5 prevented cases (1 model)
nervous system (al2)	4 extra cases (1 model)
abdominal wall defects (al49)	1 to 2 extra cases (3 models)
eye anomaly (al10)	1 to 3 extra cases (4 models)
congenital heart defects (al17)	10 to 23 prevented cases (3 models)
atrial septum defect (al22)	9 to 16 prevented cases (3 models)
other limb anomaly (RG13)	4 to 9 prevented cases (4 models)
respiratory (al34)	5 prevented cases (1 model)
Miconazole (1 treatment course, local formulations only)	
respiratory (al34)	**22 to 34 extra cases (7 models)**

other specified congenital malformations of kidney (Q638)	**21 to 37 extra cases (5 models)**
other "other anomaly" (RG14)	23 extra cases (1 model)
hypospadia (al59)	20 to 21 extra cases (3 models)
eye anomaly (al10)	11 to 14 extra cases (4 models)
other congenital heart defects (RG01)	**10 to 24 prevented cases (5 models)** or 35 extra cases (1 model)
other urinary anomaly (RG10)	25 to 34 extra cases (2 models) or 7 prevented cases (1 model)
Severe congenital heart defect (al97)	23 to 25 extra cases (4 models) or 7 to 13 prevented cases (4 models)
genital (al58)	23 to 24 extra cases (3 models) or 7.6 prevented cases (1 model)
limb (al61)	**18 to 50 prevented cases (5 models)**
other limb anomaly (RG13)	**6 to 39 prevented cases (10 models)**
all anomalies (al1)	130 prevented cases (1 model)
other digestive system anomaly (RG03)	10 prevented cases (2 models)
other genital anomaly (RG11)	7 prevented cases (1 model)
Nystatin (1 treatment course, systemic formulations only)	
all anomalies (al1)	**139 to 396 extra cases (14 models)**
congenital heart defects (al17)	**38 to 240 extra cases (8 models)**
atrial septum defect (al22)	**44 to 110 extra cases (7 models)**
ventricular septum defect (al21)	**12 to 85 extra cases (8 models)**
digestive system (al40)	**14 to 95 extra cases (16 models)**
other digestive system anomaly (RG03)	**9 to 105 extra cases (24 models)**
Metronidazole (1 treatment course, local formulations only)	
all anomalies (al1)	**165 to 216 extra cases (5 models)**
limb (al61)	**39 to 111 extra cases (8 models)**
al67 or "congenital deformity of hip, unspecified" (RG12)	**43 to 56 extra cases (6 models)**
other limb anomaly (RG13)	**31 to 59 extra cases (7 models)**
congenital heart defects (al17)	61 to 114 extra cases (2 models)
atrial septum defect (al22)	45 extra cases (1 model)
digestive system (al40)	42 extra cases (2 models)
other congenital malformations of tongue (Q383)	27 extra cases (2 models)
congenital hydronephrosis (al55)	17 to 22 extra cases (3 models)
other genital anomaly (RG11)	14 to 18 extra cases (3 models)
Severe congenital heart defect (al97)	**23 to 50 extra cases (7 models)** or 6 prevented cases (2 models)
other congenital heart defects (RG01)	35 to 57 extra cases (4 models) or 14 prevented cases (1 model)
genital (al58)	31 to 32 extra cases (2 models) or 10 prevented cases (1 model)
hypospadia (al59)	24 to 26 extra cases (2 models) or 7 prevented cases (1 model)
other urinary anomaly (RG10)	6 to 7 prevented cases (2 models) or 31 extra cases (1 model)
respiratory (al34)	6 to 13 prevented cases (3 models)

other obstructive defects of renal pelvis and ureter (Q623)	5 prevented cases (2 models)
other "other anomaly" (RG14)	5 prevented cases (1 model)
eye anomaly (al10)	2 to 5 prevented cases (2 models)
Metronidazole (1 treatment course, systemic formulations only)	
all anomalies (al1)	**42 to 117 extra cases (5 models)**
congenital skin disorders (al81)	**8 to 23 extra cases (14 models)**
ventricular septum defect (al21)	18 extra cases (1 model)
Severe congenital heart defect (al97)	12 extra cases (1 model)
ear, face and neck (al15)	10 extra cases (1 model)
other obstructive defects of renal pelvis and ureter (Q623)	8 to 10 extra cases (3 models)
other congenital malformations of tongue (Q383)	7 extra cases (2 models)
ACTIVE CONTROLS	
Carbamazepine (28-day treatment)	
all anomalies (al1)	**155 to 260 extra cases (10 models)**
digestive system (al40)	**44 to 58 extra cases (6 models)**
other digestive system anomaly (RG03)	**32 to 61 extra cases (23 models)**
other specified congenital malformations of kidney (Q638)	**30 to 64 extra cases (9 models)**
other obstructive defects of renal pelvis and ureter (Q623)	**29 to 35 extra cases (5 models)**
abdominal wall defects (al49)	**9 to 37 cases (6 models)**
congenital heart defects (al17)	114 to 137 extra cases (3 models)
urinary (al52)	88 extra cases (1 model)
atrial septum defect (al22)	71 to 99 extra cases (4 models)
other urinary anomaly (RG10)	46 extra cases (2 models)
respiratory (al34)	44 extra cases (2 models)
congenital hydronephrosis (al55)	30 to 33 extra cases (3 models)
club foot – talipes equinovarus (al66)	19 to 20 extra cases (2 models)
Isotretinoin (28-day treatment, local formulations only)	
other urinary anomaly (RG10)	**62 to 91 cases (9 models)**
digestive system (al40)	173 to 179 extra cases (2 models)
other congenital malformations of tongue (Q383)	86 to 87 extra cases (2 models)
other digestive system anomaly (RG03)	74 to 164 extra cases (4 models)
club foot – talipes equinovarus (al66)	32 to 33 extra cases (2 models)
Isotretinoin (28-day treatment, systemic formulations only)	
nervous system (al2)	**68 to 1895 extra cases (13 models)**
ear, face and neck (al15)	**54 to 279 extra cases (19 models)**
Valproic acid (28-day treatment)	
all anomalies (al1)	**196 to 485 extra cases (28 models)**
congenital heart defects (al17)	**87 to 201 extra cases (15 models)**
atrial septum defect (al22)	**81 to 112 extra cases (5 models)**
al67 or "congenital deformity of hip, unspecified" (RG12)	**62 to 78 extra cases (5 models)**
respiratory (al34)	**39 to 55 extra cases (13 models)**
nervous system (al2)	**33 to 64 extra cases (10 models)**
abdominal wall defects (al49)	**13 to 28 extra cases (18 models)**
ventricular septum defect (al21)	47 to 54 extra cases (3 models)

hip dislocation or dysplasia (al67)	70 extra cases (1 model)
congenital skin disorders (al81)	43 to 73 extra cases (3 models)
congenital malformation of kidney, unspecified (Q639)	52 to 65 extra cases (4 models)
abdominal wall defects incl. interventions (RG04)	43 extra cases (1 model)
other “other anomaly” (RG14)	27 to 33 extra cases (3 models)

For detailed visual overview of all “adjusted(2)” model results on congenital anomaly risks associated to drug exposure , please see Sections 15.3.1 – 15.3.35 and Sections 15.3.36 – 15.3.45 for Amendment 2 and Amendment 1 results, respectively, with separate sub-sections by various alternative defnitions / subgroups of malformations. For justifications of the evaluated malformation subgroups, please see Annex 3.1.4. of Protocol Amendment 2; and also Annex 3.1 of Protocol Amendment 1. A full tabular summary of all Amendment 2 and Amendment 1 logistic regression models on congenital anomalies is available in separate files (see Section 15.1).

10.4.3. Regression models on low birtweight

These analyses have been introduced into the study by Protocol Amendment 2. Effects on birthweight were analysed using three alternative indicators: birthweight below 2500g (binary analysis), birthweight below 2000g (binary analysis), or numeric birthweight data in grams. For binary and numeric outcomes, a set of logistic and linear regression models has been pre-specified in the protocol, respectively. Drug exposure is expressed in treatment cure numbers, as pre-specified in Protocol Amendment 2. For details, please see Section 9.8.3. All results of univariate and multivariate regression models are tabulated in Section 15.4. Main findings from fully adjusted models are summarized below.

10.4.3.1. Low birthweight defined as birthweight below 2,500g

Maternal residence was a strong predictor of low birthweight in all analyses, with increased odds of low birthweight in micro-regions of low socioeconomic status "Deprived" (OR 1.28, 95%CI 1.23 – 1.32 in the main analysis) and "Most deprived" (OR 1.70, 95%CI 1.62 – 1.78 in the main analysis). The socioeconomic status of "Most deprived requiring complex intervention" was associated with a risk similar to the latter one (OR 1.69, 95%CI 1.62 – 1.75). Urban residence of the mother was a protective factor (OR 0.89, 95%CI 0.87 – 0.91).

In the first trimester, butoconazole tended to be associated with increased risk of low birthweight: in the main analysis, the odds ratio for low birthweight after first butoconazole treatment was 1.35 (95%CI 0.997 – 1.83). Even though this finding did not reach statistical significance, the trend was notable and this effect could be statistically significant in a larger sample size. An increase in the risk of low birthweight was consistently observed in all sensitivity analyses on first trimester butoconazole exposure. In contrast, a statistically significant protective effect was observed for clotrimazole in the first trimester either in the main analysis (first clotrimazole treatment: OR 0.73, 95%CI 0.57 – 0.93) and in sensitivity analyses 1 (clotrimazole exposure: OR 0.72, 95%CI 0.58 – 0.88)) and 2 (first clotrimazole exposure: OR 0.69, 95%CI 0.54 – 0.87).

No significant drug effects were observed in the second trimester. In the third trimester, a significant protective effect was found both for butoconazole and clotrimazole, (main analysis, first treatment: butoconazole OR 0.45 (95%CI 0.31 – 0.65) vs. clotrimazole OR 0.61 (0.52 – 0.71); second treatment: butoconazole OR 0.22 (95%CI 0.06 – 0.90) vs. clotrimazole OR 0.60 (0.44 – 0.82). Accordingly, only sensitivity analyses where third trimester exposure were included in the models are considered relevant.

10.4.3.2. Low birthweight defined as birthweight below 2,000g

Low socioeconomic status of the microregion of maternal residence, and it's rural status were associated with increased risk of low birthweight below 2,000 gram. Non-significant trends for increased risk with butoconazole and decreased risk with clotrimazole were observed in the first trimester. No significant drug effects were observed in the second trimester. In the third trimester, a significant protective effect was found both for butoconazole and clotrimazole (sensitivity analysis 4, first treatment: butoconazole OR 0.32 (95%CI 0.16 – 0.65) vs. clotrimazole OR 0.44 (0.32 – 0.60).

10.4.3.3. Linear regression models on birthweight

In sensitivity analysis 8, "Deprived", "Most deprived", and "Most deprived requiring complex interventions" micro-regional socioeconomic indicators of maternal residence were associated with 48 gram (95%CI 43 – 53g), 110 gram (95%CI 102 – 118g), and 140 gram (133 – 146g) lower average birthweight than "normal" socioeconomic status of maternal residence, respectively. In addition, rural residence accounted for an additional 25g average decrease (95%CI 21 – 29g).

First trimester butoconazole exposure was associated with a non-significant decrease in birthweight (first treatment: 40 gram average decrease, 95%CI 88g decrease to 7g increase). First trimester clotrimazole exposure was statistically significantly associated with increased birthweight (first treatment: 33g average increase in birthweight, 95%CI 3 – 62 g). No significant drug effects were observed in the second trimester. In the third trimester, a significant increase in birthweight was found both for butoconazole and clotrimazole exposed pregnancies, with nominal advantage of butoconazole (sensitivity analysis 8, first treatment: butoconazole +82g (95%CI 46 – 118g) vs. clotrimazole +55g (95%CI 37 – 74g); second treatment: butoconazole +126g (95%CI 28 – 224g) vs. clotrimazole +73g (95%CI 38 – 108g)). The third dose of clotrimazole was associated with an increase in birthweight (+163g, 95%CI 67 – 259g) whereas the additional effect of the third butoconazole dose was not significant (+125g, 95%CI -150 – 401g).

10.5. Other analyses

Several sensitivity analyses were planned and conducted for the spontaneous abortion, congenital anomaly, and low birthweight models. To support the complex interpretation of main and sensitivity analyses on the same pregnancy risk, all sensitivity analyses together with their results are described in those sections describing the main analyses.

10.6. Adverse events / adverse reactions

The Sponsor encouraged 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 to their data management standards and regulations.

The results provided to the Sponsor and other parties have contained group 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 is made available to the competent authorities.

11. Discussion

This was the first study with the intention to determine pregnancy outcomes, pregnancy periods, drug exposure, pregnancy risks and confounding factors solely from the OEP database. In this pioneering exercise, the original study protocol failed to identify most mother – offspring pairs, since it did not match the transient and permanent social security numbers of the investigated children, resulting in the loss of medical follow-up of about 440 000 live births. Moreover, the exact hierarchy of rules for redundant and conflicting pregnancy outcome codes has not been defined in the original protocol, making pregnancy outcomes ambiguous in cases with multiple outcome records. Accordingly, as justified in Protocol Amendment 2, the study has not been analysed as planned in the original protocol. Instead, all descriptive statistics and statistical analyses (including the sensitivity analyses) are conducted according to Protocol Amendment 2 and Protocol Amendment 1.

11.1. Key results

11.1.1. Key results on spontaneous abortion risk

This study identified 128,156 spontaneous abortions in Amendment 2 analyses and 128,104 spontaneous abortions in Amendment 1 analyses – the difference between these numbers was minimal (<0.05%) and could be explained by Amendment 2 changes in the definition of pregnancies with congenital anomalies (due to the application of pre-specified hierarchy rules in cases with conflicting pregnancy outcome indicators).

For comparison, the Hungarian Central Statistical Office recorded 122,151 foetal deaths in the study time period (2005-2011), where foetal death included spontaneous abortion, ectopic pregnancy, and stillbirth. The aggregated number of these pregnancy outcomes was 142,086 and 142,034 in our Amendment 2 and Amendment 1 analyses, respectively. The slightly higher than expected number of "foetal death" in our study may be explained by incomplete reporting of medically identified and coded spontaneous abortions to the Hungarian Central Statistical Office. The potential impact of redundant reporting to the OEP database (i.e. multiple relevant codes submitted for the same pregnancy outcome in the same pregnancy) was visually assessed as shown in Figures 10.2.4.A, 10.2.4.B, and 10.2.4.E. Accordingly, the pre-specified threshold of 84 days for redundant reporting of the same spontaneous abortion was most probably adequate (assuming minimum 4 weeks for regeneration + 8 weeks to detect a second spontaneous abortion in the same mother).

Interestingly, a high number of pregnancies with unknown outcomes have been identified in our study (162,075 pregnancies both in the Amendment 1 and Amendment 2 analyses). These unknown pregnancy outcomes were most probably not live births or stillbirths as they relate to mothers without evidence of either a live birth (in the previous 12 weeks or in the next 32 weeks) or a still birth (in the previous 12 weeks or in the next 26 weeks compared to the date of the unknown pregnancy outcome). In a pre-specified sensitivity analysis of spontaneous abortion risk (S6), it was assumed that all unknown pregnancy outcomes were spontaneous abortions. This assumption implies that the true number of spontaneous abortions was 290,179 in our study, which is more than twice higher than the number of foetal deaths registered at the Hungarian Central Statistical Office in the investigated time period (122,151 recorded cases). Such an extent of under-reporting of spontaneous abortions to the Hungarian Central Statistical Office would be surprising but might be explained by the methodology of data collection (a dedicated data form must be filled and submitted by the relevant hospital personnel to the Hungarian Central Statistical Office on each of the spontaneous abortion cases – see section "Magzati halálozási lap" at https://www.ksh.hu/2016_torveny__altal_elrendelt_adatgyujtesek). Furthermore, we cannot

exclude that a few thousands of unknown pregnancy outcomes may have resulted in live births or stillbirths in non-OEP financed private clinic settings in Hungary, as collection of such data exceeds the scope of the OEP database and this study.

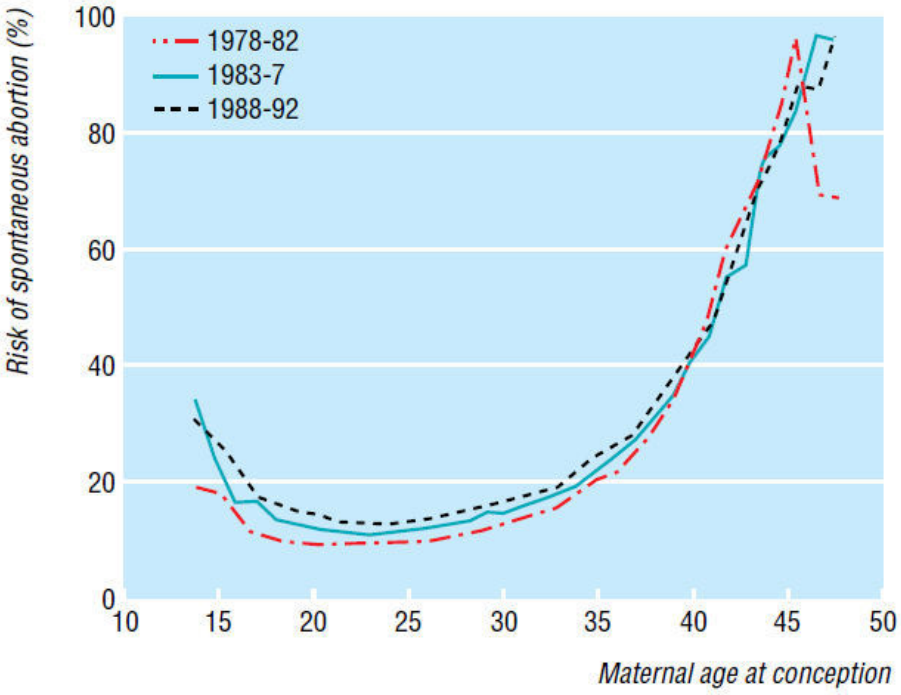
The results of the co-primary analyses on SA risk are summarized in **Table 10.S**. (Section 10.4.1), these analyses did not provide evidence for butoconazole exposure to increase the risk of spontaneous abortions.

Similarly, butoconazole was not associated with increased risk of spontaneous abortion in either of the pre-planned Amendment 1 and Amendment 2 sensitivity analyses – except for Sensitivity analyses 6, where an adjusted(2) odds ratio of 1.36 (95%CI 1.30-1.43) was associated with at least one butoconazole dose (Amendment 1) and an adjusted(2) odds ratio of 1.32 (95%CI 1.27-1.38) was associated with one butoconazole cure (Amendment 2). In these S6 analyses, all unidentified pregnancy outcomes were assumed to be spontaneous abortions, which was a pessimistic approach as discussed above. On the other hand, butoconazole was shown to be associated with a significantly lowered risk of spontaneous abortion in sensitivity analyses 2 (where the exposure window was narrowed to the last 30 days before spontaneous abortions): the adjusted(2) odds ratio of a spontaneous abortion associated with at least one butoconazole dose and with one butoconazole cure was 0.836 (95%CI 0.72-0.97) and 0.864 (95%CI 0.75-0.99) in these analyses, respectively. Similarly, butoconazole was associated with a significantly lowered risk of spontaneous abortion in sensitivity analysis 5 (where only late spontaneous abortions with reported AFP screening tests were considered): the adjusted(2) odds ratio of a spontaneous abortion associated with at least one butoconazole dose or associated with one butoconazole cure was 0.6375 (95%CI 0.43-0.94), and 0.643 (95%CI 0.45-0.92) in these analyses, respectively.

Maternal age is a recognized risk factor for spontaneous abortion, with a characteristic U-shape, i.e. slightly increased risk in ages younger than 20 years and a steep increase in risk above 35-40 years as described in a previous population-based study in Denmark investigating ~1,200,000 pregnancies (Figure 11.1.1.A, {Nybo Andersen, 2000 #30}). Reading the plotted values, the odds to spontaneous abortion were about 20/80 = 0.25 in ages before 20, 10/90 = 0.1 in the 20-30 years age group, and 60/40= 1.5 in the 40-45 age group in that study, respectively. Accordingly, selecting the 20-30 years age group as reference, the odds ratio of spontaneous abortion was 0.25/0.1 = 2.5 in ages before 20 years, and 1.5/0.1 = 15 in the 40-45 years age group. Our study found a similar U-shaped risk function for maternal age, with odds ratios of ~2 and ~8 in the 15-19 years and 40-45 years age groups, respectively (for details, see section 10.4.1.4). This finding is reinforcing the appropriateness of pregnancy outcome determination in the OEP database.

Figure 11.A. Risk of spontaneous abortion according to maternal age at conception, stratified according to calendar period in a previous population based study in Denmark.

Source: {Nybo Andersen, 2000 #30}.



Our study included active controls, i.e. drugs reported to be associated with increased risk of spontaneous abortion. Maternal exposure to non-aspirin NSAIDs have been reported to be associated with increased risk of spontaneous abortion {Li, 2003 #62}{Nielsen, 2004 #61}{Nakhai-Pour, 2011 #27}. Specifically, use of diclofenac (OR 3.09, 95% CI 1.96–4.87), naproxen (OR 2.64, 95% CI 2.13–3.28), celecoxib (OR 2.21, 95% CI 1.42–3.45), ibuprofen (OR 2.19, 95% CI 1.61–2.96) and rofecoxib (OR 1.83, 95% CI 1.24–2.70) alone, and combinations thereof (OR 2.64, 95% CI 1.59–4.39), were all associated with increased risk of spontaneous abortion in the Nakhai-Pour study. These results have been previously criticized claiming that a filled prescription does not always mean drug exposure; and that important risk factors were neglected / not captured in the analyses {Clark, 2011 #11}{Schiavetti, 2004 #63}. Clark requested to add maternal and paternal smoking and maternal BMI to the Nakhai model, referring to a study {Blanco-Munoz, 2009 #42} that did not show a significant effect of maternal or paternal smoking on miscarriage risk (with a borderline significance only when both parents were smoker) and did not include maternal BMI in its adjusted odds ratio calculations on smoking effect. Sciavetti {Schiavetti, 2004 #63} requested to add magnetic field exposure and the number of drugs during pregnancy to the Li model {Li, 2003 #62}, as known confounders. It seems that none of the published spontaneous abortion case-control studies succeeded to integrate all of the identified confounders so far. Maternal BMI was neither included e.g. in the Schiavetti paper; and neither Schiavetti nor Clark included e.g. paternal age as a potential confounder {de la Rochebrochard, 2002 #41} in their analyses. Although Schiavetti stressed its importance in 2004, exposure to magnetic fields continues to be hardly included in miscarriage studies as a confounding factor – and studies with negative findings have never been criticised yet on this occasion. Since we lack an "ideal" model integrating all known confounders into a single equation, we argue that the "realistic" approach (i.e. case-control studies considering only a limited, practically feasible set of potential confounders) is an accepted, widely used, and valuable way of risk factor evaluation and evidence generation. Furthermore, by definition only those independent risk factors are confounders of the association of a certain drug intake and spontaneous abortion, which are also associated with the drug intake itself. Thus the possibility of confounding needs to be carefully assessed in each specific case. Instead of a technocratic rejection of any positive findings in these less-than-ideal studies, the generated new pieces of evidence shall be carefully integrated into the current knowledge – not forgetting their intrinsic limitations.

Our study showed a statistically significant association of spontaneous abortions to previous exposure to systemic ibuprofen, systemic indomethacin, systemic naproxen, systemic diclofenac, and also to local diclofenac. Similarly to previous studies, this association was stronger when a shorter drug exposure period was evaluated before spontaneous abortion (or a comparable index date in controls) in sensitivity analyses 1 and 2. Note that in the main analysis a 120-day exposure window was analysed, whereas the exposure period was narrowed to 60 days and to 30 days in sensitivity analyses 1 and 2, respectively. Odds ratios for spontaneous abortion were consistently higher in these sensitivity analyses than in the main analysis, except for local diclofenac. For details, please see Section 10.4.1.3. These positive findings with active controls are reinforcing the validity of our study to evaluate the spontaneous abortion risks associated with drug exposure based on the OEP database.

Of the investigated gynaecology anti-infective drugs, we have found a significant association of systemic metronidazole exposure to increased risk of spontaneous abortion, while locally administered metronidazole was found to be associated with a decreased risk of spontaneous abortion. This apparent contradiction in our findings may be explained by differences in the ratio of therapeutic benefits and systemic exposure across locally and systemically administered metronidazole products. Surprisingly, a statistically significant protective effect was found for clotrimazole, albeit clotrimazole has been reported to be associated with increased risk of spontaneous abortion in a previous case-control study {Rosa, 1987 #35}.

Sensitivity analysis 5 (S5) may have a specific relevance since this analysis is limited to pregnancies with a valid AFP screening test, an obligatory pregnancy investigation in Hungary scheduled after 16 completed weeks of pregnancy. Accordingly, this sensitivity analysis informs on the risk of late spontaneous abortions (beyond 16 weeks of pregnancy). In S5, an increased risk of spontaneous abortion was found to be associated with systemic diclofenac (Amendment 2, OR 95%CI 1.0031 – 1.0216 by DOTs) and with systemic metronidazole (Amendment 2, OR 95%CI 1.002 – 1.192 by DOTs). A consistently decreased risk of spontaneous abortion was found in S5 sensitivity analyses for butoconazole (Amendment 1 OR 95%CI 0.4328 – 0.9390; Amendment 2 OR 95%CI 0.4292 – 0.9148 by DOTs and 0.4486 – 0.9216 by treatment cures). Clotrimazole was associated with a decreased risk of spontaneous abortion in S5 analysis per Protocol Amendment 1 (OR 95%CI 0.7566 – 0.9945), but not per Protocol Amendment 2 (OR 95%CI 0.88-1.05).

11.1.2. Key results on congenital anomaly risk

Our study initially planned to evaluate the overall rate of congenital anomalies, and the rate of two specific anomaly groups with preclinical safety concerns for butoconazole (cleft palate and abdominal wall defects), in relation to drug exposure in all relevant exposition windows as recommended by the relevant CHMP guidance {EMEA/CHMP, 2005 #17}: first month, second month, third month, second and third month pooled, first trimester, and after first trimester. For this purpose, the first day of pregnancy (defined as the first day of last menses) was to be determined. The first day of pregnancy is not recorded in the OEP database, but it could be reliably tracked back from the date of an obligatory investigation in Hungary at week 16 (see Sections 9.1.2. and 10.2.1). Accordingly, the relevant exposition windows could be identified for the vast majority of the pregnancies.

The greatest challenge in our study was to separate the congenital anomaly cases from healthy live births based on solely the OEP database records. In Protocol Amendment 1, an extensive list of relevant interventions, diseases, and diagnosis related group codes was applied, to identify as

many congenital anomaly cases as possible. In Amendment 1 analyses, 39 – 48% of live births were identified as congenital anomaly cases, which rate was about one order of magnitude higher than expected from the national registry (see Section 10.3.3). Due to the high number of false positive cases, no conclusions could be drawn from Amendment 1 analyses about overall anomaly rates. In sensitivity analyses of specific code groups on cleft palate (sensitivity analysis 6) and abdominal wall defects (sensitivity analysis 7), neither of the investigated gynecology anti-infective drugs was associated with an increased risk, whereas active controls carbamazepine and systemic isotretinoin were associated with a statistically increased risk of abdominal wall defects in various exposure windows in the first trimester (see Section 15.3.43).

In Protocol Amendment 2, a more sophisticated approach was developed for the identification of true positive congenital anomaly cases: 1) a shortened anomaly code list was adapted from EUROCAT; 2) mild anomalies (as specified by EUROCAT) were excluded from all analyses; 3) outpatient reports were excluded from sensitivity analyses; and 4) beyond the analysis of overall anomaly rate, EUROCAT-specified and custom code subgroups have been investigated (similarly to Protocol Amendment 1 CA sensitivity analyses 6 and 7). For the selection of custom code subgroups, the expected study power was considered as detailed in Protocol Amendment 2 Annex 3.1.4. Given that cases were defined in 35 alternative ways; 1 main + 8 sensitivity analyses applied to all definitions; 6 exposure windows for 13 drug groups were investigated; 3 levels of model adjustment were applied; and gynecology drug exposure unit was either the days of therapy (DOTs) or the number of treatment cures, all together 35 x 9 x 6 x 13 x 3 x 2 = 147,420 pieces of logistic regression models were composed on the risk of drug esposure in Amendment 2 analyses. To reduce this complexity, only results of the fully adjusted models are used for study conclusions, and sensitivity analyses with irrealistic number of cases are neglected (see Sections 15.3.1 – 15.3.35). The pre-defined co-primary analysis did not show an increased risk of congenital anomalies with butoconazole. No formal correction to multiple comparisons have been done in the secondary / post-hoc analyses. Accordingly, any positive finding must be interpreted carefully, considering the number and the strength of positive / negative signals across multiple sensitivity analyses / exposure periods for a certain drug/malformation association. In the secondary analyses focusing on either cleft lip/palate or abdominal wall defects, butoconazole showed statistically significant positive signals in some sensitivity analyses in some time periods, while not in several others with relevant statistical power, as detailed in Section 10.4.2.2. Importantly, all of the investigated gynecology drugs showed statistically significant increase in the risk of some congenital anomalies – which is not surprising if we consider the chances for false positive signals due to the high number of models. However, by chance, a similar number of significant findings for increased and reduced risk would be expected, which was not the case for any investigated drug in our study. It was apparent that findings of decreased risk were outnumbered by findings of increased risk when gynecology anti-infective drugs were considered. Moreover, for active controls, none of the significant findings indicated a decreased risk associated with drug exposure. To rank the identified gynecology anti-infective drugs in terms of their safety, the number of anomaly definitions or the number of regression models with positive findings alone is not a relevant basis, for the following reasons: 1) the different congenital anomaly definitions reflect different disease groups of various severity; 2) a statistically significant signal may reflect a numerically small or large increase in the odds ratio, with high or low uncertainty; and 3) the baseline odds (what is multiplied by the odds ratio in the exposed population) is highly heterogenous across the various anomalies. Therefore, to allow more relevant comparisons across gynecology anti-infective drugs, we calculated the 95% CI range for the expected number of extra congenital anomaly cases in a hypothetical cohort of 10,000 women with first trimester exposure to one treatment cure (for gynecology anti-infectives) or for a 28-day treatment (for active controls), for all anomaly definitions separately. Only statistically significant results from the fully adjusted “adjusted(2)” models from sensitivity analyses with relevant number of cases were used

for this experiment, and all models for exposure after the first trimester were omitted (drug exposure after organogenesis is less relevant {Papp, 1999 #32}{EMEA/CHMP, 2006 #18}). In this hypothetical cohort, the overall rate of congenital anomalies was increased by clotrimazole, by systemic nystatin, by local and systemic metronidazole, by carbamazepine, and by valproic acid; while local miconazole and butoconazole showed a significant protective effect in some models. When only the mean odds ratio estimates of those anomalies with significant findings in at least 5 models were considered, 9-33 digestive anomalies and 4-7 eye anomalies could be attributed to butoconazole in this hypothetical cohort. For comparison, 4-14 kidney malformations, 3-8 genital anomalies, and 3-9 congenital tongue malformations could be attributed to clotrimazole; 22-34 respiratory anomalies, 21-37 kidney anomalies, and the prevention of 18-50 limb anomalies could be attributed to local miconazole; 38-240 congenital heart defects (including 44-110 atrial and 12-85 ventricular septum defects) and 14-95 digestive anomalies could be attributed to systemic nystatin; 39 to 111 limb anomalies (including 43-56 hip deformity) could be attributed to local metronidazole; and 8-23 congenital skin disorders could be attributed to systemic metronidazole. Regarding the active controls, when a 28-day cure was considered, 44-58 digestive anomalies, 30-64 kidney anomalies, and 9-37 abdominal wall defects could be attributed to carbamazepine treatment; 62-91 urinary anomalies were attributable to local isotretinoin; 68-1895 nervous system anomalies and 54-279 ear, face, and neck anomalies were attributable to systemic isotretinoin; and 87-201 congenital heart defects (including 81-112 atrial septum defects), 62-78 hip deformities, 39-55 respiratory anomalies, 33-64 nervous system anomalies, and 13-28 abdominal wall defects could be attributed to valproic acid, respectively.

The signals found for the active controls show partial overlap with their known congenital anomaly risks. Carbamazepine is known to be associated primarily with neural tube defects, and valproic acid is known to be associated with heart defect, cleft lip, neural tube defects, and also facial features (thin upper lip, flat face, and upturned nose). Epilepsy may itself be a risk factor for various congenital anomalies {Artama, 2006 #65}. Our findings confirmed a positive association of valproic acid with cardiovascular and nervous system anomalies, but did not show increased risk for cleft lip, and found additional risks in multiple models e.g. for respiratory anomalies (13 models) and abdominal wall defects (18 models). The number of pregnancies exposed to valproic acid and carbamazepine in the first trimester were 397 and 517, respectively. This low number of exposed pregnancies could prevent the detection of some anomaly risks in our study. Note that the number of first trimester butoconazole and clotrimazole exposed pregnancies was 2,699 and 12,015, respectively.

All together, first trimester exposure to one treatment with a locally administered gynecology anti-infective drug seems to be associated with an up to 0.5% increase in the risk of having a congenital anomaly, without a clearly proven safety advantage of one product over another. The additional risk associated with one treatment with systemic nystatin or metronidazole is higher (1.4 – 4% and 0.5 – 1.2%, respectively). For comparison, a 28-day treatment with carbamazepine, local isotretinoin, systemic isotretinoin, and valproic acid in the first trimester is associated with an additional congenital anomaly risk of 1.6 – 2.6%, 0.6 – 0.9%, 0.7 – 19%, and 2 – 4.9%, respectively (see Table 10.X).

11.1.3. Key results on low birthweight risk

Both numeric and categorical (categories of <2,000 g, <2,5000 g, etc) birthweight data was available for the vast majority of live births in the OEP database, allowing the analysis of low

birthweight risk. In Protocol Amendment 1 analyses, both the categorical and the continuous scale analyses suggested a significant increase in the risk of low birthweight with butoconazole, whereas a significant protective, birthweight increasing effect was observed for clotrimazole. However, these analyses did not consider potential confounders therefore must be interpreted with caution.

Protocol Amendment 2 introduced regression models for birthweight analyses, including a set of potential confounders. However, most of the known confounders in birthweight analyses can not be captured in the OEP database (for details, please see Section 9.1.3). To overcome this limitation, a quasi-randomization design was applied in Protocol Amendment 2, excluding pregnancies exposed to the prescriptions of gynecologists with non-homogeneous prescription patterns (see Section 9.1.3). Any difference between practices of gynaecologists preferring butoconazole or clotrimazole were surrogated by measurable micro-regional socioeconomic indicators. Butoconazole and clotrimazole exposed patient populations after quasi-randomization were similar to each other within socioeconomic strata as shown in Section 10.2.6, without any clear trend by drug exposure. The results of Protocol Amendment 2 analyses showed a non-significant trend for increased risk of treatment with butoconazole in the first trimester and a significant protective effect for clotrimazole. In the third trimester, a significant protective effect was found both for butoconazole and clotrimazole. In the second trimester, no statisticaly significant effects were observed.

11.2. Limitations

Although the randomised and double blinded prospective study design represents the highest standard in human health related evidence generation on efficacy and safety of medications, such studies in pregnant women are feasible only in exceptional cases (where the study serves the best interest of both mother and infant), due to ethical considerations {EMEA/CHMP, 2005 #17}. Furthermore, safety of meadications cannot be completely investigated in trials because of the sample size limitations. Observational epidemiological studies in the form of past authorization safety studies have an important role in phamacovigilance. The case-control study design is an accepted and recommended approach for the investigation of drug effects on pregnancy outcomes in the postmarketing phase {EMEA/CHMP, 2005 #17}. For our study, a retrospective analysis was planned to avoid the time-consuming process of building a pregnancy registry prospectively. To ensure and check the validity of the study design, multiple active control drugs were included in the spontaneous abortion case-control study and in the teratogenicity case-control study.

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.

Regarding a potential recall bias in our study: records on drug exposure and the investigated confounders in the OEP database accumulated continuously, preceding the pregnancy outcome and hence, they were not affected by increased awareness in cases vs. controls. All filled prescriptions were recorded in the database prospectively, i.e. there was no retrospective data collection on drug exposure. However, the database was incomplete in terms of inpatient drug use, and did not contain data on non-prescription drugs. Therefore the study was not informed about these types of drug exposure. 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. Confounding factors e.g. diabetes or in vitro fertilisation were also looked for at the level of ICD, OENO and HBCS codes. All butoconazole, miconazole, nystatin, and metronidazole containing products, as well as active controls in the congenital anomaly models are prescription drugs in Hungary 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. 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).

To minimize selection bias, all recognized pregnancy outcomes with identified mother-offspring pairs (where relevant) were included in our study. 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 neither included in the OEP database. The

use of private healthcare services is restricted to a small fraction of the population in Hungary in general, however, the use of private gynecology services is more frequent.

Data source of the current study was the OEP database. Key features and limitations of this database are summarized in Table 11.A.

Table 11.A. Key features and limitations of the OEP database in the context of drug safety studies in pregnancy.

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 outpatient visits and investigations (except for general practitioner visits).	No coverage for patients with lack of insurance, or use of 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.	Not reported or undiagnosed (minor or major) malformations; not detected early spontaneous abortions; dilution by high numbers of minor congenital anomalies.
Birthweight data: Is routinely collected, allowing the investigation of potential drug effects on risk of low birthweight.	Important confounders (e.g. maternal BMI, smoking, etc) are not captured in the OEP database
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. Nevertheless, the calculated pregnancy duration of ~280 days was highly consistent with the typical duration of 40 weeks.
Exposure data: All filled prescriptions are recorded in the database in real time, , i.e. there is no retrospective data collection on drug exposure. Therefore, recall bias is low.	Non-prescription drugs are not included in the database; inpatient drug use is not recorded in the database; filled prescriptions do not always mean medicine intake.
Confounding factors: Several confounding factors included (maternal age, confounding drug use, maternal diabetes, in vitro fertilisation, previous pregnancy outcomes in the last 4 years, etc.).	No data on some potential confounders (e.g. maternal smoking, acute fever, employment status, pregnancy outcomes more than 4 years before).

It is acknowledged that a filled prescription does not always mean medicine intake. However, analysis of filled prescriptions is an acknowledged and frequently applied approach to monitor patient drug use in the real-life clinical setting.

Potential confounders without relevant data in the OEP database (e.g. maternal BMI and smoking, fever-related influenza or common cold, employment status, use of selected OTC drugs) were not included in the logistic regression models. It is not expected that these factors show correlations both with the pregnancy outcomes and with the exposure to gynecology anti-infectives. Thus they are not likely to be confounders in our case. The effect of random error was kept low by the large sample size (around 1 100 000 pregnancy outcomes in the OEP database).

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. To avoid the dilution of congenital anomalies of particular interest, targeted sensitivity analyses were planned on concerns raised by preclinical butoconazole studies; and the over-inclusive definitions of malformations were refined by Protocol Amendment 2.

To deal with the uncertainty of the first day of pregnancy, sensitivity analyses with alternative Day 1 estimates (±2 weeks) were conducted. The original estimate was highly consistent with the expected duration of pregnancy. Note also that several time periods of pregnancy were investigated in parallel in the congenital anomaly and low birthweight analyses.

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

Note that all of the statistical analyses, including sensitivity analyses and confounding factors are prospectivly defined in the protocol; that the study protocol has been 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 has 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 included almost 1 100 000 pregnancy outcomes, of which 2716 pregnancies were exposed to butoconazole in the first trimester: 14 stillbirths without foetal defects; and 2702 or 2703 live births in Amendment 2 and Amendment 1 analyses, respectively.

11.3. Interpretation

This was the first study with the intention to determine pregnancy outcomes, pregnancy periods, drug exposure, and confounding factors solely from the OEP database. The presented OEP-based approach may be useful also for the investigation of other drugs authorised after 1996.

11.3.1. Interpretation of findings on spontaneous abortion risk

We have conducted dedicated case-control analyses on the risk of spontaneous abortion in butoconazole-exposed pregnancies (first human data in this respect). The study has investigated multiple anti-infective gynaecology products in the same setting, allowing a comparative assessment of the butoconazole results. Maternal age and NSAIDs as active control drugs were shown to be associated with increased risk of spontaneous abortion as expected, confirming the validity of the design of our study. Butoconazole exposure was not associated with increased risk of spontaneous abortion in any of the Amendment 2 and Amendment 1 analyses, except for sensitivity analyses 6 when all unidentified pregnancy outcomes were assumed to be spontaneous abortions. On the other hand, a significant decrease in SA risk was associated with butoconazole when the exposure period was narrowed to 30 days before outcome (sensitivity analyses 2) and when only late spontaneous abortions were considered (sensitivity analyses 5). Altogether, first trimester exposure to butoconazole seems to be not associated with an increased risk of spontaneous abortion.

Of the investigated gynaecological anti-infective drugs, systemic metronidazole exposure was associated with increased risk of spontaneous abortion, while locally administered metronidazole was associated with a decreased risk of spontaneous abortion. This apparent contradiction in our findings may be explained by different ratio of therapeutic benefits and systemic exposure by locally and systemically administered metronidazole products.

Surprisingly, a statistically significant protective effect was found for clotrimazole in the main analysis and in sensitivity analyses S1, S2, S3, S4, and S6, albeit clotrimazole has been reported to be associated with increased risk of spontaneous abortion in a previous case-control study {Rosa, 1987 #35}.

11.3.2. Interpretation of findings on congenital anomaly risk

We found that the OEP database is suitable for the identification of the relevant pregnancy periods / exposure windows for population-level pregnancy safety studies. Moreover, our study established technical definitions for 35 alternative EUROCAT congenital anomaly subgroups, yielding anomaly rates from the OEP database which were consistent with official rates reported to the Hungarian Congenital Anomaly Registry in the selected sensitivity analyses. Clear positive signals were identified for most investigated active controls, suggesting that the study is sensitive enough to investigate the increased risk of congenital anomalies associated with certain drug exposures – as long as sufficient drug exposure occurred in the study period. The developed methodology can be used for the safety investigation of prescription pharmaceuticals in pregnant women in Hungary.

This study focused on the safety of butoconazole and therapeutic controls (other gynecology anti-infective drugs). The pre-specified co-primary analyses did not show any increased risk with butoconazole. A wide range of pre-planned secondary and post-hoc analyses were conducted focusing on the combination of various anomalies, sensitivity analyses, exposure windows, drugs, exposure units, and model adjustment levels. No multiplicity correction was applied to these analyses. Not surprisingly, some of the models showed statistically significant drug effects. If these findings were false signals by chance, a similar proportion of increased and decreased risk signals would be expected. However, signals of increased risk dominated across all investigated gynecology anti-infective drugs, showing that some increase in congenital anomaly rates can be associated with the use of all investigated products. To rank these products by their safety in terms of congenital anomaly rates, a hypothetical cohort of 10,000 pregnant women was generated with first trimester exposure, and anomaly rates were calculated for this cohort for all investigated

drugs. Our results suggest that first trimester exposure to one treatment cycle with a locally administered gynecology anti-infective drug is associated with an up to 0.5% increase in the risk of having a congenital anomaly, without a clearly proven safety advantage of one product over another. The additional risk associated to one treatment with systemic nystatin or metronidazole is higher (1.4 – 4% and 0.5 – 1.2%, respectively). For comparison, a 28-day treatment with carbamazepine, local isotretinoin, systemic isotretinoin, and valproic acid in the first trimester is associated with an additional congenital anomaly risk of 1.6 – 2.6%, 0.6 – 0.9%, 0.7 – 19%, and 2 – 4.9%, respectively.

In summary, our study could not exclude the risk of increased congenital anomaly rates with butoconazole, but found that a similar amount of increased risk is apparently present when locally administered butoconazole, clotrimazole, miconazole, or metronidazole products are applied for vaginal infections in pregnant women in the first trimester. This apparent increase in the risk of congenital anomalies is up to 0.5% with these products.

11.3.3. Interpretation of findings on low birthweight

A low birthweight preventive effect of clotrimazole treatment against vaginal candidiasis have been described previously (Banhidy et al., 2009; Czeizel et al., 2004; Czeizel et al., 2007). This was the first study comparing butoconazole and clotrimazole in this respect. Our study showed a statistically significant birthweight decrease and increase in pregnancies exposed to butoconazole and clotrimazole in the first trimester, respectively, in the descriptive analyses in Amendment 1. The Amendment 2 analyses introduced a quasi-randomization design and the protective effect of clotrimazole was confirmed, showing an almost statistically significant trend for increasing risk for low birthweight with butoconazole in the first trimester. However, in the third trimester, a significant protective effect was found both for butoconazole and clotrimazole. In the second trimester, no statisticaly significant effects were observed.

11.4. Generalisability

The study findings are intended to be generalized to the European population.

12. Other information

Not applicable.

13. Conclusion

This study was the first to identify pregnancy outcomes, pregnancy time periods, and drug safety in pregnancy in a population-level study in Hungary, solely based on the healthcare payer OEP database records. The developed methodology was validated with active controls in the spontaneous abortion and congenital anomaly analyses. Our study reinforced the results of previous studies showing that various NSAID drugs significantly increase the risk of spontaneous abortions when administered in early pregnancy (systemic diclofenac, ibuprophen, indomethacin, and naproxen). Maternal age was also be shown to be a risk factor for spontaneous abortion as expected. Among the active controls in the congenital anomaly models, carbamazepine and valproic acid exposures were associated with obviously increased overall rate of congenital anomalies, and several positive findings were observed in sensitivity analyses with all of the included active controls when specific types of congenital anomalies were considered (see Section 10.4.2).

Our results suggest that first trimester exposure to butoconazole is not associated with an increased risk of spontaneous abortion, but most probably can be a risk factor for low birthweight, and a slight increase in the risk of congenital anomalies can not be excluded. In comparison, first trimester clotrimazole exposure was shown to be significantly protective both against spontaneous abortions and low birthweight. Clotrimazole may also slightly increase the risk of congenital anomalies. Topical miconazole products are also available in Hungary as another locally administered treatment alternative for vaginal candidiasis. In our study, first trimester local miconazole exposure was not associated with a significant effect on spontaneous abortions, but the Amendment 1 descriptive analyses showed a statistically significant association with low birthweight. Local miconazole may also slightly increase the risk of congenital anomalies.

After the first trimester, butoconazole was found to be as safe as clotrimazole in terms of low birthweight, and it was the only gynecology anti-infective drug showing a statistically significant protective effect against spontaneous abortion in pregnancies after AFP screening (week 16) in the Amendment 2 analyses.

Due to reproductive toxicity in animals, butoconazole is currently contraindicated in Hungary in the first trimester of pregnancy and also in women of childbearing potential, unless adequate contraception is used. In light of the results of our study, this strict limitation of use reflects a careful and conservative approach in favour of patient safety.

The developed methodology of this study may support further research on the investigation of drug safety research questions in pregnancy.

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15. Appendices

15.1. List of stand-alone documents

Number	Document content	Filename and location
1	Study protocol (original)	15_1_1.pdf, uploaded to ENCEPP
2	Study protocol (Amendment 1) clean and tracked in MS Word / PDF	15_1_2.zip, available from the Sponsor upon request. The clean pdf file is uploaded to ENCEPP.
3	Study protocol (Amendment 2) clean and tracked in MS Word / PDF	15_1_3.zip, available from the Sponsor upon request. The clean pdf file is uploaded to ENCEPP.
4	Tabular summary of Amendment 1 results on congenital anomaly risks (MS Excel)	15_1_4.xlsx, available from the Sponsor upon request.
5.	Tabular summary of Amendment 2 results on congenital anomaly risks (MS Excel)	15_1_5.xlsx, available from the Sponsor upon request.
6.	Analysis package for spontaneous abortions (R scripts and input files)	15_1_6.zip, available from the Sponsor upon request.
7.	Analysis package for congenital anomalies (R scripts, input and output files)	15_1_7.zip, available from the Sponsor upon request.
8.	English proofread translation of the description of all included BNO/ICD, OENO, and HBCS codes	15_1_8.pdf, uploaded to ENCEPP site

15.2. Detailed results on spontaneous abortion

15.2.1. Detailed results on spontaneous abortion (Amendment 2, by number of cures)

Table.15.A. Main analysis of spontaneous abortions (Amendment 2, gynecology anti-infective exposure expressed in cure numbers)

Variable	Controls N = 492 424	Cases N = 127 079	OR (95% CI)* crude	adjusted (1)	adjusted (2)
Type of gynecology anti-infectives					
none	453 768 (79.18%)	119 345 (20.82%)	1 (reference)	1 (reference)	1 (reference)
butoconazole	4 549 (80.46%)	1 105 (19.54%)	0.9487 (0.8942-1.0065)	0.9687 (0.9115-1.0294)	1.0511 (0.9893-1.1168)
miconazole (local)	14 042 (81.66%)	3 153 (18.34%)	0.8727 (0.8415-0.905)	0.9187 (0.8228-1.0259)	0.9599 (0.8584-1.0734)
miconazole (systemic)	NA	NA	NA	NA	NA
clotrimazole	18 652 (88.64%)	2 391 (11.36%)	0.6173 (0.598-0.6372)	0.6472 (0.6268-0.6682)	0.6923 (0.6705-0.7148)
nystatin (local)	NA	NA	NA	NA	NA
nystatin (systemic)	36 (72%)	14 (28%)	1.0578 (0.8889-1.2589)	1.1015 (0.9247-1.3122)	1.1355 (0.954-1.3515)
metronidazole (local)	14 603 (81.52%)	3 311 (18.48%)	0.883 (0.8519-0.9152)	0.9304 (0.834-1.0379)	0.9388 (0.8404-1.0488)
metronidazole (systemic)	3 883 (68.8%)	1 761 (31.2%)	1.4034 (1.3491-1.4599)	1.4994 (1.438-1.5634)	1.5284 (1.4654-1.5941)
Type of non-aspirin NSAIDs					
none	471 778 (79.77%)	119 641 (20.23%)	1 (reference)	1 (reference)	1 (reference)
diclofenac (local)	923 (68.83%)	418 (31.17%)	1.0131 (1.0099-1.0164)	1.0028 (0.9993-1.0062)	1.003 (0.9994-1.0065)
diclofenac (systemic)	17 364 (74.12%)	6 062 (25.88%)	1.0204 (1.0186-1.0222)	1.018 (1.0161-1.02)	1.0217 (1.0198-1.0237)
naproxen (local)	NA	NA	NA	NA	NA
naproxen (systemic)	2 639 (68.37%)	1 221 (31.63%)	1.0172 (1.0152-1.0192)	1.0146 (1.0126-1.0167)	1.0146 (1.0125-1.0167)
celecoxib	10 (100%)	(0%)	1.0197 (0.9879-1.0526)	1.0101 (0.9734-1.0481)	1.0119 (0.9768-1.0483)
ibuprofen (local)	NA	NA	3.875 (0.5458-27.5091)	2.7043 (0.319-22.9251)	2.4105 (0.251-23.1497)
ibuprofen (systemic)	26 (100%)	(0%)	0.9959 (0.9034-1.0978)	1.0094 (0.9134-1.1154)	1.0283 (0.9306-1.1362)
rofecoxib	NA	NA	0.3969 (0.001-156.8777)	0.4039 (0.0009-174.1749)	0.4263 (0.0009-193.3399)
indomethacin (local)	NA	NA	0.0066 (0->1000)	0.0014 (0->1000)	0.002 (0->1000)
indomethacin (systemic)	155 (67.98%)	73 (32.02%)	1.0813 (1.0454-1.1184)	1.0584 (1.0195-1.0987)	1.0693 (1.0294-1.1108)
Maternal age at index date					

15-19	20 629 (73.73%)	7 350 (26.27%)	2.0435 (1.9846-2.1041)	2.0301 (1.9715-2.0904)	1.917 (1.8613-1.9743)
20-24	66 199 (80.69%)	15 839 (19.31%)	1.3723 (1.3436-1.4015)	1.3671 (1.3385-1.3963)	1.3193 (1.2916-1.3477)
25-29	177 749 (85.15%)	30 992 (14.85%)	1 (reference)	1 (reference)	1 (reference)
30-34	166 639 (81.89%)	36 857 (18.11%)	1.2685 (1.2477-1.2897)	1.2656 (1.2448-1.2867)	1.2284 (1.2081-1.249)
35-39	53 774 (68.6%)	24 613 (31.4%)	2.6251 (2.5749-2.6763)	2.6089 (2.5589-2.6599)	2.549 (2.4998-2.5992)
40-45	7 434 (39.41%)	11 428 (60.59%)	8.8167 (8.5424-9.0997)	8.6737 (8.4033-8.9528)	8.5031 (8.236-8.7789)

Table 15.B. Sensitivity analysis 1 of spontaneous abortions: drug exposure period narrowed to 60 days before index date (Amendment 2, gynecology anti-infective exposure expressed in cure numbers).

Variable	Controls N = 492 424	Cases N = 127 079	OR (95% CI)* crude	adjusted (1)	adjusted (2)
Type of gynecology anti-infectives					
none	466 732 (79.2%)	122 605 (20.8%)	1 (reference)	1 (reference)	1 (reference)
butoconazole	1 866 (79.68%)	476 (20.32%)	0.9921 (0.9058-1.0866)	1.0347 (0.9424-1.136)	1.0475 (0.9537-1.1506)
miconazole (local)	8 588 (83.35%)	1 716 (16.65%)	0.7752 (0.7379-0.8145)	0.9887 (0.8503-1.1498)	1.0407 (0.892-1.2143)
miconazole (systemic)	NA	NA	NA	NA	NA
clotrimazole	14 870 (90.41%)	1 578 (9.59%)	0.5232 (0.5023-0.5449)	0.5552 (0.5329-0.5784)	0.599 (0.5749-0.624)
nystatin (local)	NA	NA	NA	NA	NA
nystatin (systemic)	11 (100%)	(0%)	1.1982 (0.8976-1.5994)	1.2677 (0.9409-1.7078)	1.3151 (0.9692-1.7843)
metronidazole (local)	8 996 (83.3%)	1 804 (16.7%)	0.7795 (0.7426-0.8183)	0.758 (0.6527-0.8803)	0.7426 (0.6374-0.8652)
metronidazole (systemic)	1 224 (56.67%)	936 (43.33%)	2.071 (1.9395-2.2115)	2.3002 (2.1455-2.4662)	2.3891 (2.2269-2.5631)
Type of non-aspirin NSAIDs					
none	487 333 (79.76%)	123 688 (20.24%)	1 (reference)	1 (reference)	1 (reference)
diclofenac (local)	404 (64.64%)	221 (35.36%)	1.0188 (1.0134-1.0242)	1 (0.9936-1.0064)	1.001 (0.9945-1.0075)
diclofenac (systemic)	4 227 (61.19%)	2 681 (38.81%)	1.0568 (1.053-1.0605)	1.0512 (1.0474-1.0551)	1.0566 (1.0527-1.0606)
naproxen (local)	NA	NA	NA	NA	NA
naproxen (systemic)	527 (47.74%)	577 (52.26%)	1.0416 (1.0375-1.0457)	1.0365 (1.0322-1.0408)	1.036 (1.0317-1.0404)
celecoxib	NA	NA	1.0732 (0.9821-1.1728)	1.0535 (0.9468-1.1723)	1.0622 (0.9564-1.1797)
ibuprofen (local)	NA	NA	7.75 (0.7027-85.4691)	4.6015 (0.3471-61.0081)	3.6197 (0.2502-52.3779)

ibuprofen (systemic)	NA	NA	1.4319 (0.5918-3.4648)	1.4274 (0.5843-3.4875)	1.5886 (0.6482-3.8934)
rofecoxib	NA	NA	0.4803 (0.0061-37.7064)	0.4899 (0.0061-39.3402)	0.4529 (0.0003-599.5412)
indomethacin (local)	NA	NA	0.0448 (0->1000)	0.0182 (0->1000)	0.0113 (0->1000)
indomethacin (systemic)	26 (46.43%)	30 (53.57%)	1.2166 (1.1274-1.3129)	1.1784 (1.0804-1.2853)	1.1937 (1.0939-1.3026)
Maternal age at index date					
15-19	20 629 (73.73%)	7 350 (26.27%)	2.0435 (1.9846-2.1041)	2.0263 (1.9678-2.0866)	1.9553 (1.8985-2.0139)
20-24	66 199 (80.69%)	15 839 (19.31%)	1.3723 (1.3436-1.4015)	1.3669 (1.3383-1.3962)	1.336 (1.3078-1.3648)
25-29	177 749 (85.15%)	30 992 (14.85%)	1 (reference)	1 (reference)	1 (reference)
30-34	166 639 (81.89%)	36 857 (18.11%)	1.2685 (1.2477-1.2897)	1.2639 (1.2431-1.285)	1.2043 (1.1844-1.2246)
35-39	53 774 (68.6%)	24 613 (31.4%)	2.6251 (2.5749-2.6763)	2.6007 (2.5508-2.6515)	2.4545 (2.4069-2.5029)
40-45	7 434 (39.41%)	11 428 (60.59%)	8.8167 (8.5424-9.0997)	8.6402 (8.3706-8.9185)	8.2189 (7.9601-8.4861)

Table 15.C. Sensitivity analysis 2 of spontaneous abortions: drug exposure period narrowed to 30 days before index date (Amendment 2, gynecology anti-infective exposure expressed in cure numbers).

Variable	Controls N = 492 424	Cases N = 127 079	OR (95% CI)*		
			crude	adjusted (1)	adjusted (2)
Type of gynecology anti-infectives					
none	475 428 (79.29%)	124 205 (20.71%)	1 (reference)	1 (reference)	1 (reference)
butoconazole	1 086 (83.03%)	222 (16.97%)	0.8162 (0.7143-0.9326)	0.8624 (0.7526-0.9883)	0.864 (0.7533-0.9908)
miconazole (local)	6 066 (85.45%)	1 033 (14.55%)	0.6649 (0.6241-0.7084)	1.0903 (0.8987-1.3228)	1.1448 (0.9386-1.3961)
miconazole (systemic)	NA	NA	NA	NA	NA
clotrimazole	9 436 (89.81%)	1 071 (10.19%)	0.5338 (0.5074-0.5615)	0.5653 (0.5371-0.5951)	0.6135 (0.5828-0.6458)
nystatin (local)	NA	NA	NA	NA	NA
nystatin (systemic)	NA	NA	0.8472 (0.4134-1.7361)	0.8988 (0.4334-1.8638)	0.9578 (0.4578-2.0038)
metronidazole (local)	6 424 (85.51%)	1 089 (14.49%)	0.6623 (0.6225-0.7047)	0.5741 (0.4739-0.6954)	0.5636 (0.463-0.6861)
metronidazole (systemic)	741 (53.12%)	654 (46.88%)	2.3167 (2.128-2.5222)	2.7435 (2.5064-3.0029)	2.8623 (2.6127-3.1357)
Type of non-aspirin NSAIDs					
none	490 465 (79.62%)	125 528 (20.38%)	1 (reference)	1 (reference)	1 (reference)

diclofenac (local)	210 (63.44%)	121 (36.56%)	1.0224 (1.0138-1.031)	0.9953 (0.985-1.0057)	0.996 (0.9856-1.0066)
diclofenac (systemic)	1 602 (57.69%)	1 175 (42.31%)	1.0701 (1.0638-1.0764)	1.0625 (1.056-1.0689)	1.0678 (1.0612-1.0745)
naproxen (local)	NA	NA	NA	NA	NA
naproxen (systemic)	176 (37.77%)	290 (62.23%)	1.0581 (1.0512-1.0651)	1.0511 (1.0438-1.0583)	1.0506 (1.0433-1.0579)
celecoxib	NA	NA	1.0701 (0.9316-1.2291)	1.0334 (0.8811-1.2119)	1.0463 (0.9002-1.2161)
ibuprofen (local)	NA	NA	7.75 (0.7027-85.4691)	4.59 (0.3458-60.9171)	3.6218 (0.25-52.4724)
ibuprofen (systemic)	NA	NA	52.4148 (0->1000)	64.8655 (0->1000)	68.3798 (0->1000)
rofecoxib	NA	NA	0.9112 (0.5172-1.6053)	0.8859 (0.3484-2.2525)	0.8942 (0.3517-2.2736)
indomethacin (local)	NA	NA	0.0739 (0->1000)	0.0483 (0->1000)	0.0492 (0->1000)
indomethacin (systemic)	10 (34.48%)	19 (65.52%)	1.3563 (1.1979-1.5355)	1.2886 (1.1284-1.4715)	1.3051 (1.1431-1.4902)
Maternal age at index date					
15-19	20 629 (73.73%)	7 350 (26.27%)	2.0435 (1.9846-2.1041)	2.0316 (1.973-2.092)	1.9678 (1.9105-2.0267)
20-24	66 199 (80.69%)	15 839 (19.31%)	1.3723 (1.3436-1.4015)	1.3687 (1.34-1.3979)	1.3417 (1.3134-1.3706)
25-29	177 749 (85.15%)	30 992 (14.85%)	1 (reference)	1 (reference)	1 (reference)
30-34	166 639 (81.89%)	36 857 (18.11%)	1.2685 (1.2477-1.2897)	1.2653 (1.2446-1.2864)	1.199 (1.1792-1.2192)
35-39	53 774 (68.6%)	24 613 (31.4%)	2.6251 (2.5749-2.6763)	2.608 (2.558-2.6589)	2.4323 (2.3851-2.4803)
40-45	7 434 (39.41%)	11 428 (60.59%)	8.8167 (8.5424-9.0997)	8.698 (8.4268-8.9779)	8.196 (7.938-8.4625)

Table 15.D. Sensitivity analysis 3 of spontaneous abortions: controls include all live births and stillbirths (Amendment 2, gynecology anti-infective exposure expressed in cure numbers).

Variable	Controls N = 496 204	Cases N = 127 079	OR (95% CI)* crude	adjusted (1)	adjusted (2)
Type of gynecology anti-infectives					
none	457 366 (79.31%)	119 345 (20.69%)	1 (reference)	1 (reference)	1 (reference)
butoconazole	4 572 (80.54%)	1 105 (19.46%)	0.9508 (0.8963-1.0087)	0.971 (0.9138-1.0319)	1.0538 (0.9919-1.1196)
miconazole (local)	14 113 (81.74%)	3 153 (18.26%)	0.8749 (0.8436-0.9073)	0.9221 (0.8258-1.0295)	0.963 (0.8612-1.0768)
miconazole (systemic)	NA	NA	NA	NA	NA
clotrimazole	18 715 (88.67%)	2 391 (11.33%)	0.6192 (0.5999-0.6392)	0.6491 (0.6287-0.6702)	0.694 (0.6722-0.7165)
nystatin (local)	NA	NA	NA	NA	NA

nystatin (systemic)	36 (72%)	14 (28%)	1.0593 (0.8902-1.2606)	1.1028 (0.9259-1.3137)	1.1365 (0.9549-1.3526)
metronidazole (local)	14 678 (81.59%)	3 311 (18.41%)	0.8851 (0.854-0.9174)	0.9298 (0.8335-1.0372)	0.9386 (0.8403-1.0485)
metronidazole (systemic)	3 917 (68.99%)	1 761 (31.01%)	1.4017 (1.3475-1.458)	1.4959 (1.4348-1.5596)	1.5233 (1.4607-1.5886)
Type of non-aspirin NSAIDs					
none	475 342 (79.89%)	119 641 (20.11%)	1 (reference)	1 (reference)	1 (reference)
diclofenac (local)	934 (69.08%)	418 (30.92%)	1.0129 (1.0097-1.0161)	1.0026 (0.9991-1.006)	1.0026 (0.9992-1.0061)
diclofenac (systemic)	17 542 (74.32%)	6 062 (25.68%)	1.0202 (1.0183-1.022)	1.0178 (1.0159-1.0197)	1.0214 (1.0195-1.0234)
naproxen (local)	NA	NA	NA	NA	NA
naproxen (systemic)	2 669 (68.61%)	1 221 (31.39%)	1.017 (1.015-1.0189)	1.0144 (1.0123-1.0165)	1.0143 (1.0122-1.0164)
celecoxib	11 (100%)	(0%)	1.0192 (0.9876-1.0519)	1.0096 (0.9734-1.0472)	1.0116 (0.9767-1.0477)
ibuprofen (local)	NA	NA	3.9047 (0.55-27.7203)	2.7298 (0.3226-23.1001)	2.4304 (0.2537-23.2811)
ibuprofen (systemic)	26 (100%)	(0%)	0.9964 (0.904-1.0984)	1.01 (0.9141-1.116)	1.0286 (0.931-1.1365)
rofecoxib	NA	NA	0.3973 (0.001-157.3789)	0.4042 (0.0009-174.6693)	0.4265 (0.0009-193.57)
indomethacin (local)	NA	NA	0.0067 (0->1000)	0.0014 (0->1000)	0.002 (0->1000)
indomethacin (systemic)	157 (68.26%)	73 (31.74%)	1.0806 (1.0449-1.1176)	1.0576 (1.019-1.0978)	1.0686 (1.0289-1.1099)
Maternal age at index date					
15-19	20 953 (74.03%)	7 350 (25.97%)	2.0234 (1.9652-2.0833)	2.0102 (1.9523-2.0698)	1.8973 (1.8423-1.954)
20-24	66 839 (80.84%)	15 839 (19.16%)	1.3669 (1.3384-1.3961)	1.3617 (1.3332-1.3908)	1.3134 (1.2858-1.3417)
25-29	178 770 (85.23%)	30 992 (14.77%)	1 (reference)	1 (reference)	1 (reference)
30-34	167 744 (81.99%)	36 857 (18.01%)	1.2674 (1.2467-1.2885)	1.2645 (1.2437-1.2855)	1.2273 (1.2071-1.2479)
35-39	54 329 (68.82%)	24 613 (31.18%)	2.6132 (2.5633-2.6641)	2.5969 (2.5472-2.6476)	2.5376 (2.4887-2.5875)
40-45	7 569 (39.84%)	11 428 (60.16%)	8.7092 (8.4395-8.9874)	8.5678 (8.302-8.8422)	8.4 (8.1374-8.6711)

Table 15.E. Sensitivity analysis 4 of spontaneous abortions: replication of the published sensitivity analysis of the Rosa study. (Amendment 2, gynecology anti-infective exposure expressed in cure numbers).

Variable	Controls N = 393 823	Cases N = 87 449	OR (95% CI)* crude	adjusted (1)	adjusted (2)
Type of gynecology anti-infectives					
none	364 736 (81.82%)	81 047 (18.18%)	1 (reference)	1 (reference)	1 (reference)
butoconazole	4 385 (81.81%)	975 (18.19%)	1.0014 (0.941-1.0657)	1.003 (0.9407-1.0693)	1.0435 (0.9787-1.1126)
miconazole (local)	10 555 (80.06%)	2 629 (19.94%)	1.1035 (1.0604-1.1484)	0.9201 (0.8169-1.0364)	0.9452 (0.8381-1.066)
miconazole (systemic)	NA	NA	NA	NA	NA
clotrimazole	12 159 (86.2%)	1 946 (13.8%)	0.8037 (0.777-0.8314)	0.8373 (0.8092-0.8663)	0.8748 (0.8456-0.9051)
nystatin (local)	NA	NA	NA	NA	NA
nystatin (systemic)	40 (75.47%)	13 (24.53%)	1.0301 (0.8722-1.2165)	1.0595 (0.8963-1.2523)	1.0842 (0.9183-1.28)
metronidazole (local)	10 891 (79.82%)	2 754 (20.18%)	1.1277 (1.0841-1.1731)	1.1859 (1.0537-1.3348)	1.1893 (1.0553-1.3402)
metronidazole (systemic)	4 320 (75.18%)	1 426 (24.82%)	1.2444 (1.1948-1.296)	1.2449 (1.1926-1.2994)	1.2603 (1.2071-1.3159)
Type of non-aspirin NSAIDs					
none	369 144 (81.91%)	81 532 (18.09%)	1 (reference)	1 (reference)	1 (reference)
diclofenac (local)	977 (73.07%)	360 (26.93%)	1.0118 (1.0086-1.0151)	1.0055 (1.0021-1.0089)	1.0056 (1.0022-1.0091)
diclofenac (systemic)	20 786 (81.24%)	4 800 (18.76%)	1.0068 (1.005-1.0087)	1.0044 (1.0024-1.0063)	1.0069 (1.005-1.0089)
naproxen (local)	NA	NA	NA	NA	NA
naproxen (systemic)	3 318 (77.02%)	990 (22.98%)	1.0107 (1.0088-1.0127)	1.0086 (1.0065-1.0106)	1.0082 (1.0062-1.0103)
celecoxib	13 (100%)	(0%)	1.0166 (0.9881-1.0459)	1.0072 (0.975-1.0404)	1.0077 (0.9759-1.0406)
ibuprofen (local)	NA	NA	9.0072 (0.8167-99.3343)	5.3615 (0.3997-71.9143)	4.444 (0.2947-67.0103)
ibuprofen (systemic)	41 (100%)	(0%)	0.9155 (0.784-1.069)	0.9225 (0.7906-1.0763)	0.9356 (0.8043-1.0884)
rofecoxib	NA	NA	0.4345 (0.0006-294.6425)	0.4443 (0.0007-296.8996)	0.4583 (0.0007-306.3025)
indomethacin (local)	NA	NA	0.0012 (0->1000)	0.0014 (0->1000)	0.0016 (0->1000)
indomethacin (systemic)	190 (74.8%)	64 (25.2%)	1.0524 (1.0167-1.0892)	1.0358 (0.9982-1.0749)	1.0436 (1.0053-1.0833)
Maternal age at index date					
15-19	15 870 (75.93%)	5 031 (24.07%)	2.1478 (2.0743-2.2239)	2.1419 (2.0686-2.2179)	2.0551 (1.9842-2.1286)
20-24	52 331 (82.94%)	10 767 (17.06%)	1.394 (1.3592-1.4296)	1.3909 (1.3562-1.4264)	1.3596 (1.3255-1.3945)

25-29	144 475 (87.14%)	21 324 (12.86%)	1 (reference)	1 (reference)	1 (reference)
30-34	133 023 (83.91%)	25 508 (16.09%)	1.2992 (1.2739-1.325)	1.2985 (1.2732-1.3243)	1.2631 (1.2384-1.2883)
35-39	42 413 (71.47%)	16 934 (28.53%)	2.7051 (2.6439-2.7678)	2.6996 (2.6385-2.7622)	2.6239 (2.5642-2.6851)
40-45	5 711 (42.01%)	7 884 (57.99%)	9.3532 (9.0137-9.7054)	9.2882 (8.9507-9.6383)	9.128 (8.7944-9.4742)

Table 15.F. Sensitivity analysis 5 of spontaneous abortions: cases and controls restricted to pregnancies with reported AFP screening test, drug exposure in the last 16 weeks before reported date of AFP screening test. (Amendment 2, gynecology anti-infective exposure expressed in cure numbers).

Variable	Controls N = 440 917	Cases N = 5391	OR (95% CI)* crude	adjusted (1)	adjusted (2)
Type of gynecology anti-infectives					
none	398 108 (98.78%)	4 919 (1.22%)	1 (reference)	1 (reference)	1 (reference)
butoconazole	3 438 (99.25%)	26 (0.75%)	0.6281 (0.438-0.9006)	0.6408 (0.4468-0.919)	0.643 (0.4486-0.9216)
miconazole (local)	16 201 (98.66%)	220 (1.34%)	1.1171 (0.9883-1.2626)	1.0774 (0.7312-1.5876)	1.1007 (0.7434-1.6297)
miconazole (systemic)	NA	NA	NA	NA	NA
clotrimazole	22 663 (99.03%)	222 (0.97%)	0.9044 (0.8271-0.9889)	0.9292 (0.8505-1.0153)	0.9618 (0.8804-1.0507)
nystatin (local)	NA	NA	NA	NA	NA
nystatin (systemic)	26 (100%)	(0%)	0 (0->1000)	0 (0->1000)	0 (0->1000)
metronidazole (local)	17 020 (98.67%)	229 (1.33%)	1.1194 (0.9924-1.2627)	1.069 (0.7281-1.5696)	1.0641 (0.7214-1.5697)
metronidazole (systemic)	3 049 (98.51%)	46 (1.49%)	1.1848 (0.9773-1.4364)	1.1758 (0.9647-1.4332)	1.1963 (0.9821-1.4573)
Type of non-aspirin NSAIDs					
none	429 293 (98.8%)	5 225 (1.2%)	1 (reference)	1 (reference)	1 (reference)
diclofenac (local)	654 (97.9%)	14 (2.1%)	1.0099 (0.9959-1.0241)	1.0066 (0.9914-1.0221)	1.0065 (0.9917-1.0215)
diclofenac (systemic)	9 756 (98.63%)	136 (1.37%)	1.0128 (1.0034-1.0224)	1.0101 (1.0007-1.0196)	1.0123 (1.0031-1.0216)
naproxen (local)	NA	NA	NA	NA	NA
naproxen (systemic)	1 321 (98.44%)	21 (1.56%)	1.0078 (0.9962-1.0196)	1.0049 (0.9933-1.0168)	1.0047 (0.9931-1.0165)
celecoxib	NA	NA	0.608 (0.0001->1000)	0.2493 (0->1000)	0.2541 (0->1000)
ibuprofen (local)	NA	NA	NA	NA	NA
ibuprofen (systemic)	19 (100%)	(0%)	0.0031 (0->1000)	0 (0->1000)	0 (0->1000)
rofecoxib	NA	NA	0.4686 (0->1000)	0.1133 (0->1000)	0.117 (0->1000)

indomethacin (local)	NA	NA	0.0128 (0->1000)	0 (0->1000)	0 (0->1000)
indomethacin (systemic)	93 (100%)	(0%)	1.0002 (0.7653-1.3071)	0.9911 (0.7547-1.3016)	1.0042 (0.7652-1.3178)
Maternal age at index date					
15-19	16 206 (98.31%)	279 (1.69%)	2.0563 (1.806-2.3412)	2.0479 (1.7986-2.3318)	2.0204 (1.7744-2.3006)
20-24	58 546 (98.95%)	620 (1.05%)	1.2649 (1.1498-1.3915)	1.2624 (1.1475-1.3887)	1.2547 (1.1405-1.3803)
25-29	163 158 (99.17%)	1 366 (0.83%)	1 (reference)	1 (reference)	1 (reference)
30-34	151 745 (98.85%)	1 764 (1.15%)	1.3885 (1.2933-1.4906)	1.3891 (1.2939-1.4913)	1.3532 (1.2603-1.4531)
35-39	45 408 (97.68%)	1 079 (2.32%)	2.8382 (2.6187-3.0762)	2.8368 (2.6173-3.0748)	2.7573 (2.5434-2.9893)
40-45	5 854 (95.39%)	283 (4.61%)	5.7742 (5.0671-6.58)	5.7459 (5.0418-6.5485)	5.5729 (4.8886-6.353)

Table 15.G. Sensitivity analysis 6 of spontaneous abortions: cases also include pregnancies without identified pregnancy outcome. (Amendment 2, gynecology anti-infective exposure expressed in cure numbers).

Variable	Controls N = 492 424	Cases N = 268 671	OR (95% CI)* crude	adjusted (1)	adjusted (2)
Type of gynecology anti-infectives					
none	453 768 (64.72%)	247 332 (35.28%)	1 (reference)	1 (reference)	1 (reference)
butoconazole	4 549 (59.07%)	3 152 (40.93%)	1.2401 (1.1909-1.2914)	1.2603 (1.2084-1.3143)	1.3246 (1.27-1.3817)
miconazole (local)	14 042 (61.51%)	8 786 (38.49%)	1.1401 (1.1122-1.1687)	0.7751 (0.7181-0.8366)	0.7984 (0.7394-0.8622)
miconazole (systemic)	NA	NA	NA	NA	NA
clotrimazole	18 652 (75.25%)	6 134 (24.75%)	0.7164 (0.7017-0.7314)	0.7315 (0.7161-0.7472)	0.763 (0.747-0.7794)
nystatin (local)	NA	NA	NA	NA	NA
nystatin (systemic)	36 (48.65%)	38 (51.35%)	1.1196 (0.9838-1.2742)	1.1212 (0.9766-1.2872)	1.1448 (0.9967-1.3149)
metronidazole (local)	14 603 (60.5%)	9 535 (39.5%)	1.1958 (1.1673-1.2251)	1.422 (1.3195-1.5326)	1.4184 (1.3155-1.5294)
metronidazole (systemic)	3 883 (42.85%)	5 179 (57.15%)	1.7898 (1.7367-1.8445)	1.7003 (1.6472-1.7552)	1.7233 (1.6692-1.7791)
Type of non-aspirin NSAIDs					
none	471 778 (65.58%)	247 596 (34.42%)	1 (reference)	1 (reference)	1 (reference)
diclofenac (local)	923 (41.78%)	1 286 (58.22%)	1.0246 (1.0217-1.0275)	1.0098 (1.0069-1.0127)	1.0101 (1.0073-1.013)
diclofenac (systemic)	17 364 (51.18%)	16 562 (48.82%)	1.038 (1.0365-1.0395)	1.0332 (1.0317-1.0348)	1.0364 (1.0349-1.038)
naproxen (local)	NA	NA	NA	NA	NA

naproxen (systemic)	2 639 (38.1%)	4 288 (61.9%)	1.0323 (1.0306-1.034)	1.027 (1.0252-1.0287)	1.0271 (1.0254-1.0289)
celecoxib	10 (32.26%)	21 (67.74%)	1.0533 (1.0155-1.0926)	1.0437 (1.0076-1.081)	1.0421 (1.0063-1.0791)
ibuprofen (local)	NA	NA	2.7492 (0.4594-16.4533)	2.1091 (0.3146-14.1404)	1.9493 (0.279-13.6182)
ibuprofen (systemic)	26 (68.42%)	12 (31.58%)	1.0338 (0.9766-1.0943)	1.035 (0.9745-1.0993)	1.045 (0.9836-1.1102)
rofecoxib	NA	NA	0.417 (0.0131-13.2247)	0.4286 (0.0124-14.7936)	0.4379 (0.0125-15.3205)
indomethacin (local)	NA	NA	0.4528 (0.0866-2.3679)	0.4828 (0.0961-2.4255)	0.5251 (0.106-2.6016)
indomethacin (systemic)	155 (38.94%)	243 (61.06%)	1.1411 (1.1098-1.1733)	1.114 (1.0822-1.1467)	1.1239 (1.0915-1.1572)
Maternal age at index date					
15-19	20 629 (50.38%)	20 320 (49.62%)	2.7358 (2.678-2.7949)	2.7345 (2.6764-2.7938)	2.6712 (2.6142-2.7294)
20-24	66 199 (63.19%)	38 566 (36.81%)	1.6181 (1.5932-1.6433)	1.614 (1.5891-1.6392)	1.5854 (1.5609-1.6104)
25-29	177 749 (73.53%)	63 998 (26.47%)	1 (reference)	1 (reference)	1 (reference)
30-34	166 639 (69.44%)	73 336 (30.56%)	1.2223 (1.2071-1.2377)	1.2217 (1.2065-1.2372)	1.1963 (1.1813-1.2115)
35-39	53 774 (53.43%)	46 873 (46.57%)	2.421 (2.3841-2.4584)	2.4032 (2.3665-2.4405)	2.3627 (2.3264-2.3995)
40-45	7 434 (22.52%)	25 578 (77.48%)	9.5562 (9.2983-9.8213)	9.2761 (9.0247-9.5345)	9.2447 (8.9935-9.503)

15.2.2. Detailed results on spontaneous abortion (Amendment 2, by DOTs)

Table 15.H. Main analysis of spontaneous abortions (Amendment 2, all drug exposure expressed in DOTs)

Variable	Controls N = 492 424	Cases N = 127 079	OR (95% CI)* crude	adjusted (1)	adjusted (2)
Type of gynecology anti-infectives					
none	453 768 (79.18%)	119 345 (20.82%)	1 (reference)	1 (reference)	1 (reference)
butoconazole	4 549 (80.46%)	1 105 (19.54%)	0.9425 (0.885-1.0039)	0.9579 (0.8976-1.0221)	1.0493 (0.9833-1.1198)
miconazole (local)	14 042 (81.66%)	3 153 (18.34%)	0.987 (0.9833-0.9907)	0.9927 (0.9806-1.0049)	0.9972 (0.9848-1.0096)
miconazole (systemic)	NA	NA	NA	NA	NA
clotrimazole	18 652 (88.64%)	2 391 (11.36%)	0.9206 (0.9154-0.9258)	0.9281 (0.9229-0.9334)	0.9394 (0.9341-0.9447)
nystatin (local)	NA	NA	NA	NA	NA
nystatin (systemic)	36 (72%)	14 (28%)	1.0126 (0.991-1.0345)	1.0176 (0.9957-1.0401)	1.0224 (1.0003-1.0449)
metronidazole (local)	14 603 (81.52%)	3 311 (18.48%)	0.988 (0.9843-0.9916)	0.9917 (0.9799-1.0037)	0.9928 (0.9807-1.0049)
metronidazole (systemic)	3 883 (68.8%)	1 761 (31.2%)	1.1756 (1.1558-1.1957)	1.2085 (1.1871-1.2302)	1.2143 (1.1927-1.2363)
Type of non-aspirin NSAIDs					
none	471 778 (79.77%)	119 641 (20.23%)	1 (reference)	1 (reference)	1 (reference)
diclofenac (local)	923 (68.83%)	418 (31.17%)	1.0131 (1.0099-1.0164)	1.0028 (0.9993-1.0062)	1.0029 (0.9994-1.0064)
diclofenac (systemic)	17 364 (74.12%)	6 062 (25.88%)	1.0204 (1.0186-1.0222)	1.018 (1.0161-1.0199)	1.0216 (1.0197-1.0236)
naproxen (local)	NA	NA	NA	NA	NA
naproxen (systemic)	2 639 (68.37%)	1 221 (31.63%)	1.0172 (1.0152-1.0192)	1.0146 (1.0125-1.0166)	1.0145 (1.0124-1.0166)
celecoxib	10 (100%)	(0%)	1.0197 (0.9879-1.0526)	1.0101 (0.9734-1.0482)	1.0119 (0.9768-1.0483)
ibuprofen (local)	NA	NA	3.875 (0.5458-27.5091)	2.7069 (0.3193-22.9497)	2.4094 (0.2508-23.1437)
ibuprofen (systemic)	26 (100%)	(0%)	0.9959 (0.9034-1.0978)	1.007 (0.9121-1.1117)	1.0249 (0.9285-1.1314)
rofecoxib	NA	NA	0.3969 (0.001-156.8777)	0.404 (0.0009-174.2449)	0.4263 (0.0009-193.2488)
indomethacin (local)	NA	NA	0.0066 (0->1000)	0.0014 (0->1000)	0.002 (0->1000)
indomethacin (systemic)	155 (67.98%)	73 (32.02%)	1.0813 (1.0454-1.1184)	1.0585 (1.0196-1.0988)	1.0694 (1.0294-1.1109)
Maternal age at index date					
15-19	20 629 (73.73%)	7 350 (26.27%)	2.0435 (1.9846-2.1041)	2.0316 (1.973-2.092)	1.9183 (1.8625-1.9757)
20-24	66 199 (80.69%)	15 839 (19.31%)	1.3723 (1.3436-1.4015)	1.3676 (1.339-1.3969)	1.3199 (1.2921-1.3482)

25-29	177 749 (85.15%)	30 992 (14.85%)	1 (reference)	1 (reference)	1 (reference)
30-34	166 639 (81.89%)	36 857 (18.11%)	1.2685 (1.2477-1.2897)	1.2656 (1.2448-1.2867)	1.2282 (1.208-1.2488)
35-39	53 774 (68.6%)	24 613 (31.4%)	2.6251 (2.5749-2.6763)	2.6095 (2.5595-2.6605)	2.5492 (2.5-2.5994)
40-45	7 434 (39.41%)	11 428 (60.59%)	8.8167 (8.5424-9.0997)	8.6794 (8.4088-8.9587)	8.5101 (8.2428-8.7861)

Table 15.I. Sensitivity analysis 1 of spontaneous abortions: drug exposure period narrowed to 60 days before index date (Amendment 2, all drug exposure expressed in DOTs).

Variable	Controls N = 492 424	Cases N = 127 079	OR (95% CI)* crude	adjusted (1)	adjusted (2)
Type of gynecology anti-infectives					
none	466 732 (79.2%)	122 605 (20.8%)	1 (reference)	1 (reference)	1 (reference)
butoconazole	1 866 (79.68%)	476 (20.32%)	0.9841 (0.8926-1.085)	1.0193 (0.9218-1.1271)	1.0333 (0.934-1.1432)
miconazole (local)	8 588 (83.35%)	1 716 (16.65%)	0.975 (0.97-0.98)	1.0016 (0.9851-1.0184)	1.0066 (0.9896-1.0238)
miconazole (systemic)	NA	NA	NA	NA	NA
clotrimazole	14 870 (90.41%)	1 578 (9.59%)	0.8921 (0.8856-0.8986)	0.9015 (0.8949-0.9082)	0.9141 (0.9074-0.9209)
nystatin (local)	NA	NA	NA	NA	NA
nystatin (systemic)	11 (100%)	(0%)	1.0208 (0.9849-1.0581)	1.0268 (0.9896-1.0653)	1.0319 (0.9941-1.0711)
metronidazole (local)	8 996 (83.3%)	1 804 (16.7%)	0.9754 (0.9705-0.9803)	0.9694 (0.9538-0.9854)	0.9677 (0.9517-0.984)
metronidazole (systemic)	1 224 (56.67%)	936 (43.33%)	1.3931 (1.3553-1.4319)	1.4553 (1.4136-1.4983)	1.4729 (1.4302-1.5169)
Type of non-aspirin NSAIDs					
none	487 333 (79.76%)	123 688 (20.24%)	1 (reference)	1 (reference)	1 (reference)
diclofenac (local)	404 (64.64%)	221 (35.36%)	1.0188 (1.0134-1.0242)	0.9999 (0.9935-1.0063)	1.0009 (0.9944-1.0074)
diclofenac (systemic)	4 227 (61.19%)	2 681 (38.81%)	1.0568 (1.053-1.0605)	1.0512 (1.0474-1.0551)	1.0566 (1.0527-1.0606)
naproxen (local)	NA	NA	NA	NA	NA
naproxen (systemic)	527 (47.74%)	577 (52.26%)	1.0416 (1.0375-1.0457)	1.0365 (1.0322-1.0407)	1.036 (1.0317-1.0403)
celecoxib	NA	NA	1.0732 (0.9821-1.1728)	1.0536 (0.9468-1.1724)	1.0623 (0.9564-1.1799)
ibuprofen (local)	NA	NA	7.75 (0.7027-85.4691)	4.6041 (0.3472-61.0462)	3.6108 (0.2493-52.3006)
ibuprofen (systemic)	NA	NA	1.4319 (0.5918-3.4648)	1.443 (0.5896-3.5318)	1.607 (0.6545-3.9454)
rofecoxib	NA	NA	0.4803 (0.0061-37.7064)	0.4899 (0.0061-39.3437)	0.4529 (0.0003-599.5739)
indomethacin (local)	NA	NA	0.0448 (0->1000)	0.0182 (0->1000)	0.0113 (0->1000)

indomethacin (systemic)	26 (46.43%)	30 (53.57%)	1.2166 (1.1274-1.3129)	1.1806 (1.0824-1.2876)	1.196 (1.0961-1.305)
Maternal age at index date					
15-19	20 629 (73.73%)	7 350 (26.27%)	2.0435 (1.9846-2.1041)	2.0268 (1.9683-2.0871)	1.9541 (1.8972-2.0126)
20-24	66 199 (80.69%)	15 839 (19.31%)	1.3723 (1.3436-1.4015)	1.3672 (1.3385-1.3964)	1.3358 (1.3076-1.3645)
25-29	177 749 (85.15%)	30 992 (14.85%)	1 (reference)	1 (reference)	1 (reference)
30-34	166 639 (81.89%)	36 857 (18.11%)	1.2685 (1.2477-1.2897)	1.2642 (1.2434-1.2853)	1.2042 (1.1843-1.2245)
35-39	53 774 (68.6%)	24 613 (31.4%)	2.6251 (2.5749-2.6763)	2.6012 (2.5513-2.652)	2.4543 (2.4068-2.5028)
40-45	7 434 (39.41%)	11 428 (60.59%)	8.8167 (8.5424-9.0997)	8.6434 (8.3737-8.9218)	8.2265 (7.9675-8.4939)

Table 15.J. Sensitivity analysis 2 of spontaneous abortions: drug exposure period narrowed to 30 days before index date (Amendment 2, all drug exposure expressed in DOTs).

Variable	Controls N = 492 424	Cases N = 127 079	OR (95% CI)* crude	adjusted (1)	adjusted (2)
Type of gynecology anti-infectives					
none	475 428 (79.29%)	124 205 (20.71%)	1	1	1
butoconazole	1 086 (83.03%)	222 (16.97%)	0.7905 (0.6851-0.912)	0.834 (0.7201-0.9658)	0.8358 (0.7211-0.9687)
miconazole (local)	6 066 (85.45%)	1 033 (14.55%)	0.9592 (0.9529-0.9656)	1.0133 (0.9915-1.0356)	1.0177 (0.9953-1.0406)
miconazole (systemic)	NA	NA	NA	NA	NA
clotrimazole	9 436 (89.81%)	1 071 (10.19%)	0.898 (0.8898-0.9062)	0.9071 (0.8988-0.9154)	0.9208 (0.9124-0.9294)
nystatin (local)	NA	NA	NA	NA	NA
nystatin (systemic)	NA	NA	0.9691 (0.8844-1.0619)	0.9759 (0.8893-1.0709)	0.983 (0.8944-1.0805)
metronidazole (local)	6 424 (85.51%)	1 089 (14.49%)	0.9589 (0.9527-0.965)	0.9404 (0.9206-0.9606)	0.9394 (0.9191-0.96)
metronidazole (systemic)	741 (53.12%)	654 (46.88%)	1.4733 (1.4224-1.526)	1.5787 (1.5204-1.6392)	1.5988 (1.5388-1.6611)
Type of non-aspirin NSAIDs					
none	490 465 (79.62%)	125 528 (20.38%)	1 (reference)	1 (reference)	1 (reference)
diclofenac (local)	210 (63.44%)	121 (36.56%)	1.0224 (1.0138-1.031)	0.9952 (0.9849-1.0056)	0.9959 (0.9855-1.0065)
diclofenac (systemic)	1 602 (57.69%)	1 175 (42.31%)	1.0701 (1.0638-1.0764)	1.0625 (1.0561-1.0689)	1.0679 (1.0613-1.0745)
naproxen (local)	NA	NA	NA	NA	NA
naproxen (systemic)	176 (37.77%)	290 (62.23%)	1.0581 (1.0512-1.0651)	1.0511 (1.0439-1.0583)	1.0506 (1.0433-1.058)
celecoxib	NA	NA	1.0701 (0.9316-1.2291)	1.0334 (0.8812-1.2119)	1.0462 (0.9001-1.2161)
ibuprofen (local)	NA	NA	7.75 (0.7027-85.4691)	4.5931 (0.3461-60.9637)	3.6226 (0.2501-52.4673)
ibuprofen (systemic)	NA	NA	52.4148 (0->1000)	64.8806 (0->1000)	68.4129 (0->1000)
rofecoxib	NA	NA	0.9112 (0.5172-1.6053)	0.8859 (0.3484-2.2526)	0.8941 (0.3516-2.2735)
indomethacin (local)	NA	NA	0.0739 (0->1000)	0.0483 (0->1000)	0.0492 (0->1000)
indomethacin (systemic)	10 (34.48%)	19 (65.52%)	1.3563 (1.1979-1.5355)	1.2931 (1.1325-1.4766)	1.3097 (1.1472-1.4952)
Maternal age at index date					
15-19	20 629 (73.73%)	7 350 (26.27%)	2.0435 (1.9846-2.1041)	2.0325 (1.9738-2.0929)	1.9702 (1.9129-2.0292)
20-24	66 199 (80.69%)	15 839 (19.31%)	1.3723 (1.3436-1.4015)	1.369 (1.3404-1.3983)	1.3423 (1.314-1.3712)

25-29	177 749 (85.15%)	30 992 (14.85%)	1 (reference)	1 (reference)	1 (reference)
30-34	166 639 (81.89%)	36 857 (18.11%)	1.2685 (1.2477-1.2897)	1.2658 (1.245-1.2869)	1.1995 (1.1796-1.2197)
35-39	53 774 (68.6%)	24 613 (31.4%)	2.6251 (2.5749-2.6763)	2.6092 (2.5592-2.6602)	2.4334 (2.3863-2.4815)
40-45	7 434 (39.41%)	11 428 (60.59%)	8.8167 (8.5424-9.0997)	8.7017 (8.4304-8.9818)	8.1999 (7.9417-8.4665)

Table 15.K. Sensitivity analysis 3 of spontaneous abortions: controls include all live births and stillbirths (Amendment 2, all drug exposure expressed in DOTs).

Variable	Controls N = 496 204	Cases N = 127 079	OR (95% CI)*		
			crude	adjusted (1)	adjusted (2)
Type of gynecology anti-infectives					
none	457 366 (79.31%)	119 345 (20.69%)	1 (reference)	1 (reference)	1 (reference)
butoconazole	4 572 (80.54%)	1 105 (19.46%)	0.945 (0.8873-1.0065)	0.9605 (0.9002-1.0249)	1.0527 (0.9865-1.1233)
miconazole (local)	14 113 (81.74%)	3 153 (18.26%)	0.9873 (0.9835-0.991)	0.9931 (0.981-1.0054)	0.9976 (0.9853-1.01)
miconazole (systemic)	NA	NA	NA	NA	NA
clotrimazole	18 715 (88.67%)	2 391 (11.33%)	0.9211 (0.9159-0.9263)	0.9286 (0.9234-0.9339)	0.9398 (0.9345-0.9451)
nystatin (local)	NA	NA	NA	NA	NA
nystatin (systemic)	36 (72%)	14 (28%)	1.0128 (0.9913-1.0348)	1.0179 (0.9959-1.0403)	1.0226 (1.0005-1.0451)
metronidazole (local)	14 678 (81.59%)	3 311 (18.41%)	0.9882 (0.9846-0.9919)	0.9916 (0.9797-1.0036)	0.9926 (0.9806-1.0048)
metronidazole (systemic)	3 917 (68.99%)	1 761 (31.01%)	1.1752 (1.1555-1.1953)	1.2075 (1.1862-1.2291)	1.213 (1.1915-1.2349)
Type of non-aspirin NSAIDs					
none	475 342 (79.89%)	119 641 (20.11%)	1 (reference)	1 (reference)	1 (reference)
diclofenac (local)	934 (69.08%)	418 (30.92%)	1.0129 (1.0097-1.0161)	1.0026 (0.9991-1.006)	1.0026 (0.9991-1.0061)
diclofenac (systemic)	17 542 (74.32%)	6 062 (25.68%)	1.0202 (1.0183-1.022)	1.0177 (1.0158-1.0196)	1.0214 (1.0194-1.0233)
naproxen (local)	NA	NA	NA	NA	NA
naproxen (systemic)	2 669 (68.61%)	1 221 (31.39%)	1.017 (1.015-1.0189)	1.0143 (1.0122-1.0164)	1.0142 (1.0121-1.0163)
celecoxib	11 (100%)	(0%)	1.0192 (0.9876-1.0519)	1.0097 (0.9734-1.0473)	1.0116 (0.9767-1.0478)
ibuprofen (local)	NA	NA	3.9047 (0.55-27.7203)	2.7325 (0.3229-23.125)	2.4296 (0.2537-23.2707)
ibuprofen (systemic)	26 (100%)	(0%)	0.9964 (0.904-1.0984)	1.0076 (0.9127-1.1123)	1.0254 (0.929-1.1318)
rofecoxib	NA	NA	0.3973 (0.001-157.3789)	0.4043 (0.0009-174.739)	0.4263 (0.0009-193.4877)

indomethacin (local)	NA	NA	0.0067 (0->1000)	0.0014 (0->1000)	0.002 (0->1000)
indomethacin (systemic)	157 (68.26%)	73 (31.74%)	1.0806 (1.0449-1.1176)	1.0577 (1.0191-1.0979)	1.0687 (1.0289-1.11)
Maternal age at index date					
15-19	20 953 (74.03%)	7 350 (25.97%)	2.0234 (1.9652-2.0833)	2.0117 (1.9537-2.0714)	1.8993 (1.8442-1.956)
20-24	66 839 (80.84%)	15 839 (19.16%)	1.3669 (1.3384-1.3961)	1.3622 (1.3337-1.3913)	1.3141 (1.2864-1.3423)
25-29	178 770 (85.23%)	30 992 (14.77%)	1 (reference)	1 (reference)	1 (reference)
30-34	167 744 (81.99%)	36 857 (18.01%)	1.2674 (1.2467-1.2885)	1.2644 (1.2437-1.2855)	1.2274 (1.2072-1.248)
35-39	54 329 (68.82%)	24 613 (31.18%)	2.6132 (2.5633-2.6641)	2.5975 (2.5477-2.6482)	2.5386 (2.4897-2.5885)
40-45	7 569 (39.84%)	11 428 (60.16%)	8.7092 (8.4395-8.9874)	8.5733 (8.3072-8.8478)	8.4073 (8.1445-8.6787)

Table 15.L. Sensitivity analysis 4 of spontaneous abortions: replication of the published sensitivity analysis of the Rosa study. (Amendment 2, all drug exposure expressed in DOTs).

Variable	Controls N = 393823	Cases N = 87 448	OR (95% CI)* crude	adjusted (1)	adjusted (2)
Type of gynecology anti-infectives					
none	364 736 (81.82%)	81 047 (18.18%)	1 (reference)	1 (reference)	1 (reference)
butoconazole	4 385 (81.81%)	975 (18.19%)	0.9993 (0.9349-1.0681)	0.9958 (0.9298-1.0664)	1.0421 (0.9728-1.1163)
miconazole (local)	10 555 (80.06%)	2 629 (19.94%)	1.0113 (1.0072-1.0155)	0.9919 (0.9787-1.0053)	0.9943 (0.9809-1.0079)
miconazole (systemic)	NA	NA	NA	NA	NA
clotrimazole	12 159 (86.2%)	1 946 (13.8%)	0.9639 (0.9583-0.9695)	0.9706 (0.9649-0.9763)	0.9782 (0.9725-0.984)
nystatin (local)	NA	NA	NA	NA	NA
nystatin (systemic)	40 (75.47%)	13 (24.53%)	1.0087 (0.9887-1.0291)	1.0122 (0.9919-1.033)	1.0155 (0.9952-1.0362)
metronidazole (local)	10 891 (79.82%)	2 754 (20.18%)	1.013 (1.0089-1.0171)	1.0173 (1.0039-1.0308)	1.0181 (1.0045-1.0317)
metronidazole (systemic)	4 320 (75.18%)	1 426 (24.82%)	1.1172 (1.0975-1.1373)	1.1201 (1.0994-1.1412)	1.1237 (1.1028-1.1449)
Type of non-aspirin NSAIDs					
none	369 144 (81.91%)	81 532 (18.09%)	1 (reference)	1 (reference)	1 (reference)
diclofenac (local)	977 (73.07%)	360 (26.93%)	1.0118 (1.0086-1.0151)	1.0055 (1.0021-1.0089)	1.0056 (1.0022-1.0091)
diclofenac (systemic)	20 786 (81.24%)	4 800 (18.76%)	1.0068 (1.005-1.0087)	1.0043 (1.0024-1.0063)	1.0069 (1.0049-1.0088)
naproxen (local)	NA	NA	NA	NA	NA
naproxen (systemic)	3 318 (77.02%)	990 (22.98%)	1.0107 (1.0088-1.0127)	1.0085 (1.0065-1.0105)	1.0082 (1.0061-1.0102)
celecoxib	13 (100%)	(0%)	1.0166 (0.9881-1.0459)	1.0072 (0.975-1.0405)	1.0078 (0.9759-1.0406)
ibuprofen (local)	NA	NA	9.0072 (0.8167-99.3343)	5.3667 (0.4001-71.9881)	4.4512 (0.2951-67.1357)
ibuprofen (systemic)	41 (100%)	(0%)	0.9155 (0.784-1.069)	0.9213 (0.79-1.0744)	0.9339 (0.803-1.086)
rofecoxib	NA	NA	0.4345 (0.0006-294.6425)	0.4444 (0.0007-296.9344)	0.4582 (0.0007-306.2043)
indomethacin (local)	NA	NA	0.0012 (0->1000)	0.0014 (0->1000)	0.0016 (0->1000)
indomethacin (systemic)	190 (74.8%)	64 (25.2%)	1.0524 (1.0167-1.0892)	1.0358 (0.9982-1.0748)	1.0436 (1.0054-1.0833)
Maternal age at index date					
15-19	15 870 (75.93%)	5 031 (24.07%)	2.1478 (2.0743-2.2239)	2.1429 (2.0695-2.2189)	2.055 (1.9841-2.1285)
20-24	52 331 (82.94%)	10 767 (17.06%)	1.394 (1.3592-1.4296)	1.3911 (1.3565-1.4267)	1.3594 (1.3253-1.3943)
25-29	144 475 (87.14%)	21 324 (12.86%)	1 (reference)	1 (reference)	1 (reference)

30-34	133 023 (83.91%)	25 508 (16.09%)	1.2992 (1.2739-1.325)	1.2985 (1.2732-1.3243)	1.2631 (1.2384-1.2883)
35-39	42 413 (71.47%)	16 934 (28.53%)	2.7051 (2.6439-2.7678)	2.6998 (2.6386-2.7624)	2.6242 (2.5644-2.6854)
40-45	5 711 (42.01%)	7 884 (57.99%)	9.3532 (9.0137-9.7054)	9.2925 (8.9549-9.6428)	9.1328 (8.7991-9.4793)

Table 15.M. Sensitivity analysis 5 of spontaneous abortions: cases and controls restricted to pregnancies with reported AFP screening test, drug exposure in the last 16 weeks before reported date of AFP screening test. (Amendment 2, all drug exposure expressed in DOTs).

Variable	Controls N = 440 917	Cases N = 5391	OR (95% CI)* crude	adjusted (1)	adjusted (2)
Type of gynecology anti-infectives					
none	398 108 (98.78%)	4 919 (1.22%)	1 (reference)	1 (reference)	1 (reference)
butoconazole	3 438 (99.25%)	26 (0.75%)	0.6114 (0.419-0.8922)	0.6243 (0.4276-0.9114)	0.6266 (0.4292-0.9148)
miconazole (local)	16 201 (98.66%)	220 (1.34%)	1.0106 (0.9975-1.0238)	1.0106 (0.9681-1.055)	1.0126 (0.9695-1.0576)
miconazole (systemic)	NA	NA	NA	NA	NA
clotrimazole	22 663 (99.03%)	222 (0.97%)	0.9771 (0.9611-0.9932)	0.9827 (0.9667-0.9989)	0.9892 (0.9731-1.0056)
nystatin (local)	NA	NA	NA	NA	NA
nystatin (systemic)	26 (100%)	(0%)	0.6817 (0.003-152.9635)	0.5894 (0->1000)	0.5928 (0->1000)
metronidazole (local)	17 020 (98.67%)	229 (1.33%)	1.0104 (0.9977-1.0234)	1.0025 (0.961-1.0458)	1.0023 (0.9604-1.0461)
metronidazole (systemic)	3 049 (98.51%)	46 (1.49%)	1.0857 (0.9967-1.1827)	1.0878 (0.9968-1.1872)	1.0928 (1.002-1.192)
Type of non-aspirin NSAIDs					
none	429 293 (98.8%)	5 225 (1.2%)	1 (reference)	1 (reference)	1 (reference)
diclofenac (local)	654 (97.9%)	14 (2.1%)	1.0099 (0.9959-1.0241)	1.0066 (0.9914-1.0221)	1.0065 (0.9917-1.0215)
diclofenac (systemic)	9 756 (98.63%)	136 (1.37%)	1.0128 (1.0034-1.0224)	1.0101 (1.0007-1.0196)	1.0123 (1.0031-1.0216)
naproxen (local)	NA	NA	NA	NA	NA
naproxen (systemic)	1 321 (98.44%)	21 (1.56%)	1.0078 (0.9962-1.0196)	1.005 (0.9933-1.0168)	1.0048 (0.9931-1.0165)
celecoxib	NA	NA	0.608 (0.0001->1000)	0.4111 (0->1000)	0.4163 (0->1000)
ibuprofen (local)	NA	NA	NA	NA	NA
ibuprofen (systemic)	19 (100%)	(0%)	0.0031 (0->1000)	0.0015 (0->1000)	0.0015 (0->1000)
rofecoxib	NA	NA	0.4686 (0->1000)	0.2313 (0->1000)	0.2388 (0->1000)
indomethacin (local)	NA	NA	0.0128 (0->1000)	0.0001 (0->1000)	0.0002 (0->1000)

indomethacin (systemic)	93 (100%)	(0%)	1.0002 (0.7653-1.3071)	0.991 (0.7546-1.3014)	1.004 (0.7651-1.3176)
Maternal age at index date					
15-19	16 206 (98.31%)	279 (1.69%)	2.0563 (1.806-2.3412)	2.0469 (1.7977-2.3306)	2.0194 (1.7734-2.2994)
20-24	58 546 (98.95%)	620 (1.05%)	1.2649 (1.1498-1.3915)	1.2623 (1.1475-1.3886)	1.2547 (1.1405-1.3803)
25-29	163 158 (99.17%)	1 366 (0.83%)	1 (reference)	1 (reference)	1 (reference)
30-34	151 745 (98.85%)	1 764 (1.15%)	1.3885 (1.2933-1.4906)	1.3887 (1.2935-1.4909)	1.3533 (1.2603-1.4531)
35-39	45 408 (97.68%)	1 079 (2.32%)	2.8382 (2.6187-3.0762)	2.8351 (2.6157-3.0729)	2.7565 (2.5426-2.9884)
40-45	5 854 (95.39%)	283 (4.61%)	5.7742 (5.0671-6.58)	5.74 (5.0365-6.5417)	5.5693 (4.8854-6.3489)

Table 15.N. Sensitivity analysis 6 of spontaneous abortions: cases also include pregnancies without identified pregnancy outcome. (Amendment 2, all drug exposure expressed in DOTs).

Variable	Controls N = 492 424	Cases N = 268 671	OR (95% CI)* crude	adjusted (1)	adjusted (2)
Type of gynecology anti-infectives					
none	453 768 (64.72%)	247 332 (35.28%)	1 (reference)	1 (reference)	1 (reference)
butoconazole	4 549 (59.07%)	3 152 (40.93%)	1.263 (1.2096-1.3188)	1.2785 (1.2225-1.3372)	1.3508 (1.2914-1.4129)
miconazole (local)	14 042 (61.51%)	8 786 (38.49%)	1.0151 (1.0124-1.0177)	0.9697 (0.9617-0.9777)	0.9725 (0.9644-0.9806)
miconazole (systemic)	NA	NA	NA	NA	NA
clotrimazole	18 652 (75.25%)	6 134 (24.75%)	0.9472 (0.9438-0.9506)	0.9504 (0.9469-0.9539)	0.9576 (0.9541-0.9611)
nystatin (local)	NA	NA	NA	NA	NA
nystatin (systemic)	36 (48.65%)	38 (51.35%)	1.0203 (1.0034-1.0375)	1.0219 (1.0045-1.0396)	1.0252 (1.0076-1.043)
metronidazole (local)	14 603 (60.5%)	9 535 (39.5%)	1.0198 (1.0173-1.0224)	1.0422 (1.0338-1.0506)	1.0421 (1.0337-1.0506)
metronidazole (systemic)	3 883 (42.85%)	5 179 (57.15%)	1.2998 (1.2829-1.317)	1.2704 (1.2531-1.2879)	1.2758 (1.2583-1.2935)
Type of non-aspirin NSAIDs					
none	471 778 (65.58%)	247 596 (34.42%)	1 (reference)	1 (reference)	1 (reference)
diclofenac (local)	923 (41.78%)	1 286 (58.22%)	1.0246 (1.0217-1.0275)	1.0098 (1.0069-1.0126)	1.0101 (1.0072-1.013)
diclofenac (systemic)	17 364 (51.18%)	16 562 (48.82%)	1.038 (1.0365-1.0395)	1.0332 (1.0317-1.0347)	1.0363 (1.0348-1.0379)
naproxen (local)	NA	NA	NA	NA	NA
naproxen (systemic)	2 639 (38.1%)	4 288 (61.9%)	1.0323 (1.0306-1.034)	1.0269 (1.0251-1.0286)	1.0271 (1.0253-1.0288)
celecoxib	10 (32.26%)	21 (67.74%)	1.0533 (1.0155-1.0926)	1.0436 (1.0076-1.081)	1.0421 (1.0063-1.0791)
ibuprofen (local)	NA	NA	2.7492 (0.4594-16.4533)	2.1128 (0.3151-14.1659)	1.9539 (0.2796-13.652)
ibuprofen (systemic)	26 (68.42%)	12 (31.58%)	1.0338 (0.9766-1.0943)	1.0325 (0.9726-1.0961)	1.0421 (0.9812-1.1068)
rofecoxib	(NA)	(NA)	0.417 (0.0131-13.2247)	0.4288 (0.0124-14.8014)	0.4378 (0.0125-15.3287)
indomethacin (local)	NA	NA	0.4528 (0.0866-2.3679)	0.4834 (0.0962-2.4282)	0.5246 (0.1058-2.6002)
indomethacin (systemic)	155 (38.94%)	243 (61.06%)	1.1411 (1.1098-1.1733)	1.1141 (1.0823-1.1468)	1.1239 (1.0915-1.1573)
Maternal age at index date					
15-19	20 629 (50.38%)	20 320 (49.62%)	2.7358 (2.678-2.7949)	2.7367 (2.6786-2.7961)	2.6752 (2.6181-2.7335)
20-24	66 199 (63.19%)	38 566 (36.81%)	1.6181 (1.5932-1.6433)	1.6149 (1.59-1.6402)	1.5868 (1.5623-1.6118)
25-29	177 749 (73.53%)	63 998 (26.47%)	1 (reference)	1 (reference)	1 (reference)

30-34	166 639 (69.44%)	73 336 (30.56%)	1.2223 (1.2071-1.2377)	1.2217 (1.2064-1.2372)	1.1965 (1.1815-1.2117)
35-39	53 774 (53.43%)	46 873 (46.57%)	2.421 (2.3841-2.4584)	2.4037 (2.3669-2.441)	2.3632 (2.3269-2.4001)
40-45	7 434 (22.52%)	25 578 (77.48%)	9.5562 (9.2983-9.8213)	9.2805 (9.029-9.539)	9.2497 (8.9983-9.5081)

15.2.3. Detailed results on spontaneous abortion (Amendment 1, binary exposure parameters)

Table 15.O. Main analysis of spontaneous abortions (Amendment 1, binary exposure).

Variable	Controls N=493,112	Cases N=128,104	OR (95% CI)*		
			crude	adjusted (1)	adjusted (2)
Type of gynecology anti-infectives					
none	454 425 (79.06%)	120 327 (20.94%)	1 (reference)	1 (reference)	1 (reference)
butoconazole	4 553 (80.41%)	1 109 (19.59%)	0.9371 (0.8773-1.0009)	0.9535 (0.891-1.0205)	1.0517 (0.9825-1.1259)
miconazole (local)	14 056 (81.57%)	3 175 (18.43%)	0.8662 (0.833-0.9006)	0.9334 (0.8202-1.0622)	0.9809 (0.8604-1.1182)
miconazole (systemic)	(NA)	(NA)	NA	NA	NA
clotrimazole	18 663 (88.62%)	2 396 (11.38%)	0.4845 (0.4642-0.5058)	0.5174 (0.4953-0.5405)	0.5655 (0.5411-0.5909)
nystatin (local)	(NA)	(NA)	NA	NA	NA
nystatin (systemic)	36 (70.59%)	15 (29.41%)	1.6039 (0.8782-2.9295)	1.7442 (0.9352-3.2531)	2.0438 (1.0955-3.8131)
metronidazole (local)	14 618 (81.44%)	3 332 (18.56%)	0.8741 (0.8414-0.9081)	0.8949 (0.7881-1.0161)	0.9045 (0.7952-1.0287)
metronidazole (systemic)	3 889 (68.67%)	1 774 (31.33%)	1.7665 (1.6695-1.8692)	1.9497 (1.8368-2.0695)	2.002 (1.8852-2.126)
Type of non-aspirin NSAIDs					
none	472 357 (79.67%)	120 544 (20.33%)	1 (reference)	1 (reference)	1 (reference)
diclofenac (local)	942 (68.76%)	428 (31.24%)	1.7515 (1.5621-1.9638)	1.3218 (1.1703-1.4929)	1.3806 (1.2212-1.5608)
diclofenac (systemic)	17 385 (73.91%)	6 138 (26.09%)	1.3771 (1.3367-1.4187)	1.3452 (1.3043-1.3874)	1.4679 (1.4229-1.5144)
naproxen (local)	(NA)	(NA)	NA	NA	NA
naproxen (systemic)	2 641 (68.03%)	1 241 (31.97%)	1.8167 (1.6977-1.944)	1.7176 (1.6005-1.8432)	1.7707 (1.6488-1.9016)
celecoxib	10 (100%)	(0%)	1.1548 (0.3178-4.1961)	0.9312 (0.2384-3.6372)	0.9208 (0.2409-3.5196)
ibuprofen (local)	(NA)	(NA)	3.8494 (0.5422-27.3271)	2.7112 (0.3197-22.9911)	2.4559 (0.2533-23.8104)
ibuprofen (systemic)	108 (78.26%)	30 (21.74%)	1.0693 (0.7135-1.6024)	0.9882 (0.6482-1.5066)	1.1435 (0.7475-1.7492)

rofecoxib	(NA)	(NA)	0.0007 (0->1000)	0.0007 (0->1000)	0.0011 (0->1000)
indomethacin (local)	10 (100%)	(0%)	0.7699 (0.1687-3.5136)	0.6696 (0.1362-3.2911)	0.8281 (0.1706-4.0197)
indomethacin (systemic)	155 (67.1%)	76 (32.9%)	1.8879 (1.4347-2.4844)	1.6215 (1.214-2.1658)	1.7781 (1.328-2.3809)
Maternal age at index date					
15-19	20 629 (73.74%)	7 346 (26.26%)	2.0431 (1.9843-2.1038)	2.0309 (1.9723-2.0913)	1.981 (1.9234-2.0403)
20-24	66 199 (80.7%)	15 833 (19.3%)	1.3723 (1.3436-1.4016)	1.3675 (1.3388-1.3967)	1.3361 (1.3079-1.3648)
25-29	177 749 (85.16%)	30 980 (14.84%)	1 (reference)	1 (reference)	1 (reference)
30-34	166 639 (81.9%)	36 833 (18.1%)	1.2682 (1.2474-1.2893)	1.2661 (1.2453-1.2872)	1.2215 (1.2013-1.242)
35-39	53 774 (68.61%)	24 607 (31.39%)	2.6255 (2.5753-2.6767)	2.6115 (2.5614-2.6625)	2.5444 (2.4953-2.5945)
40-45	7 434 (39.41%)	11 428 (60.59%)	8.8201 (8.5457-9.1033)	8.6929 (8.4219-8.9727)	8.516 (8.2483-8.7923)

Table 15.P. Sensitivity analysis 1 of spontaneous abortions: drug exposure period narrowed to 60 days before index date (Amendment 1, binary exposure).

Variable	Controls N=493,112	Cases N=128,104	OR (95% CI)* crude	adjusted (1)	adjusted (2)
Type of gynecology anti-infectives					
none	467 404 (79.09%)	123 601 (20.91%)	1 (reference)	1 (reference)	1 (reference)
butoconazole	1 866 (79.61%)	478 (20.39%)	0.986 (0.8916-1.0904)	1.0289 (0.9275-1.1414)	1.0361 (0.9335-1.1499)
miconazole (local)	8 596 (83.24%)	1 731 (16.76%)	0.7721 (0.7329-0.8133)	1.0679 (0.8994-1.268)	1.1209 (0.9411-1.335)
miconazole (systemic)	(NA)	(NA)	NA	NA	NA
clotrimazole	14 877 (90.39%)	1 581 (9.61%)	0.4017 (0.3813-0.4232)	0.4335 (0.4112-0.4572)	0.4789 (0.454-0.5051)
nystatin (local)	(NA)	(NA)	NA	NA	NA
nystatin (systemic)	11 (100%)	(0%)	1.7497 (0.6079-5.0359)	2.157 (0.7309-6.3662)	2.5957 (0.8777-7.6767)
metronidazole (local)	9 004 (83.19%)	1 819 (16.81%)	0.7744 (0.7361-0.8148)	0.6864 (0.5798-0.8127)	0.6768 (0.57-0.8037)
metronidazole (systemic)	1 226 (56.47%)	945 (43.53%)	2.9817 (2.7385-3.2464)	3.461 (3.161-3.7894)	3.6452 (3.3265-3.9945)
Type of non-aspirin NSAIDs					
none	487 993 (79.65%)	124 645 (20.35%)	1 (reference)	1 (reference)	1 (reference)
diclofenac (local)	409 (64.41%)	226 (35.59%)	2.129 (1.8096-2.5048)	1.3146 (1.0994-1.5719)	1.3982 (1.167-1.6752)
diclofenac (systemic)	4 235 (60.87%)	2 723 (39.13%)	2.507 (2.3883-2.6317)	2.3214 (2.2064-2.4424)	2.5647 (2.4368-2.6993)
naproxen (local)	(NA)	(NA)	NA	NA	NA
naproxen (systemic)	527 (47.35%)	586 (52.65%)	4.2953 (3.8179-4.8324)	3.7132 (3.281-4.2022)	3.7757 (3.3317-4.2788)
celecoxib	(NA)	(NA)	2.5662 (0.4288-15.3581)	1.7832 (0.2585-12.3025)	2.2105 (0.3339-14.6357)
ibuprofen (local)	(NA)	(NA)	7.6987 (0.6981-84.9037)	4.6185 (0.3483-61.2326)	3.6361 (0.2516-52.5506)
ibuprofen (systemic)	18 (52.94%)	16 (47.06%)	3.4219 (1.745-6.7104)	2.8919 (1.4212-5.8846)	3.4318 (1.6797-7.0115)

rofecoxib	(NA)	(NA)	0.002 (0->1000)	0.0016 (0->1000)	0.0025 (0->1000)
indomethacin (local)	(NA)	(NA)	1.2831 (0.259-6.3573)	1.2157 (0.2202-6.7119)	1.4731 (0.2744-7.9072)
indomethacin (systemic)	26 (44.83%)	32 (55.17%)	4.7385 (2.8241-7.9507)	3.683 (2.1072-6.4369)	4.0346 (2.3044-7.0639)
Maternal age at index date					
15-19	20 629 (73.74%)	7 346 (26.26%)	2.0431 (1.9843-2.1038)	2.0255 (1.9669-2.0858)	2.0098 (1.9513-2.0701)
20-24	66 199 (80.7%)	15 833 (19.3%)	1.3723 (1.3436-1.4016)	1.3669 (1.3382-1.3962)	1.3503 (1.3218-1.3794)
25-29	177 749 (85.16%)	30 980 (14.84%)	1 (reference)	1 (reference)	1 (reference)
30-34	166 639 (81.9%)	36 833 (18.1%)	1.2682 (1.2474-1.2893)	1.2634 (1.2427-1.2845)	1.1968 (1.177-1.2169)
35-39	53 774 (68.61%)	24 607 (31.39%)	2.6255 (2.5753-2.6767)	2.6003 (2.5503-2.6511)	2.4381 (2.3908-2.4863)
40-45	7 434 (39.41%)	11 428 (60.59%)	8.8201 (8.5457-9.1033)	8.641 (8.3712-8.9196)	8.1684 (7.911-8.4343)

Table 15.Q. Sensitivity analysis 2 of spontaneous abortions: drug exposure period narrowed to 30 days before index date (Amendment 1, binary exposure).

Variable	Controls N=493,112	Cases N=128,104	OR (95% CI)* crude	adjusted (1)	adjusted (2)
Type of gynecology anti-infectives					
none	476 104 (79.18%)	125 210 (20.82%)	1 (reference)	1 (reference)	1 (reference)
butoconazole	1 086 (82.9%)	224 (17.1%)	0.7936 (0.6872-0.9165)	0.84 (0.7246-0.9737)	0.8362 (0.7208-0.97)
miconazole (local)	6 071 (85.34%)	1 043 (14.66%)	0.6585 (0.6165-0.7035)	1.2389 (0.993-1.5457)	1.2912 (1.031-1.6172)
miconazole (systemic)	(NA)	(NA)	NA	NA	NA
clotrimazole	9 442 (89.8%)	1 072 (10.2%)	0.4323 (0.4057-0.4606)	0.4632 (0.4343-0.4941)	0.5128 (0.4806-0.5472)
nystatin (local)	(NA)	(NA)	NA	NA	NA
nystatin (systemic)	(NA)	(NA)	0.5499 (0.0677-4.4695)	0.6549 (0.0793-5.411)	0.8392 (0.102-6.9016)
metronidazole (local)	6 429 (85.39%)	1 100 (14.61%)	0.6557 (0.6149-0.6992)	0.4937 (0.3973-0.6136)	0.4896 (0.3926-0.6107)
metronidazole (systemic)	742 (52.92%)	660 (47.08%)	3.4365 (3.0938-3.8171)	4.3261 (3.8646-4.8426)	4.5462 (4.0564-5.095)
Type of non-aspirin NSAIDs					
none	491 141 (79.52%)	126 516 (20.48%)	1 (reference)	1 (reference)	1 (reference)
diclofenac (local)	214 (63.31%)	124 (36.69%)	2.2316 (1.7886-2.7844)	1.1942 (0.9327-1.529)	1.2724 (0.9909-1.634)
diclofenac (systemic)	1 604 (57.29%)	1 196 (42.71%)	2.8878 (2.6788-3.1131)	2.6157 (2.4176-2.83)	2.8824 (2.6625-3.1205)
naproxen (local)	(NA)	(NA)	NA	NA	NA
naproxen (systemic)	176 (37.21%)	297 (62.79%)	6.5085 (5.4009-7.8432)	5.3382 (4.3873-6.4952)	5.3642 (4.401-6.5382)
celecoxib	(NA)	(NA)	3.8493 (0.2408-61.5416)	1.9319 (0.0798-46.7865)	2.4927 (0.1233-50.4041)
ibuprofen (local)	(NA)	(NA)	7.6987 (0.6981-84.9037)	4.5991 (0.3465-61.0392)	3.6378 (0.2509-52.7544)
ibuprofen (systemic)	(NA)	(NA)	7.6989 (1.9255-30.7841)	6.9534 (1.686-28.6768)	8.121 (1.9639-33.5813)

rofecoxib	(NA)	(NA)	0.0054 (0->1000)	0.0031 (0->1000)	0.0053 (0->1000)
indomethacin (local)	(NA)	(NA)	0.9623 (0.1076-8.6099)	0.6954 (0.064-7.551)	0.9636 (0.0934-9.9361)
indomethacin (systemic)	10 (33.33%)	20 (66.67%)	7.6997 (3.6041-16.4495)	5.2642 (2.3197-11.9466)	5.6856 (2.5081-12.8883)
Maternal age at index date					
15-19	20 629 (73.74%)	7 346 (26.26%)	2.0431 (1.9843-2.1038)	2.0309 (1.9723-2.0913)	2.0346 (1.9753-2.0956)
20-24	66 199 (80.7%)	15 833 (19.3%)	1.3723 (1.3436-1.4016)	1.3689 (1.3402-1.3981)	1.3592 (1.3305-1.3884)
25-29	177 749 (85.16%)	30 980 (14.84%)	1 (reference)	1 (reference)	1 (reference)
30-34	166 639 (81.9%)	36 833 (18.1%)	1.2682 (1.2474-1.2893)	1.265 (1.2442-1.2861)	1.1903 (1.1706-1.2104)
35-39	53 774 (68.61%)	24 607 (31.39%)	2.6255 (2.5753-2.6767)	2.6086 (2.5585-2.6596)	2.417 (2.3701-2.4648)
40-45	7 434 (39.41%)	11 428 (60.59%)	8.8201 (8.5457-9.1033)	8.698 (8.4267-8.9781)	8.1783 (7.9206-8.4444)

Table 15.R. Sensitivity analysis 3 of spontaneous abortions: controls include all live births and stillbirths (Amendment 1, binary exposure).

Variable	Controls N=496,911	Cases N=128,104	OR (95% CI)* crude	adjusted (1)	adjusted (2)
Type of gynecology anti-infectives					
none	458 041 (79.2%)	120 327 (20.8%)	1 (reference)	1 (reference)	1 (reference)
butoconazole	4 577 (80.5%)	1 109 (19.5%)	0.9393 (0.8794-1.0033)	0.9555 (0.8928-1.0225)	1.0545 (0.9851-1.1288)
miconazole (local)	14 127 (81.65%)	3 175 (18.35%)	0.8685 (0.8353-0.9031)	0.9366 (0.8232-1.0657)	0.9834 (0.8627-1.1209)
miconazole (systemic)	(NA)	(NA)	NA	NA	NA
clotrimazole	18 726 (88.66%)	2 396 (11.34%)	0.4867 (0.4662-0.5081)	0.5197 (0.4975-0.5429)	0.5677 (0.5433-0.5932)
nystatin (local)	(NA)	(NA)	NA	NA	NA
nystatin (systemic)	36 (70.59%)	15 (29.41%)	1.6163 (0.885-2.9521)	1.7575 (0.9425-3.277)	2.0612 (1.1051-3.8446)
metronidazole (local)	14 693 (81.51%)	3 332 (18.49%)	0.8764 (0.8437-0.9105)	0.8946 (0.788-1.0156)	0.9048 (0.7956-1.029)
metronidazole (systemic)	3 923 (68.86%)	1 774 (31.14%)	1.7647 (1.6679-1.8671)	1.9447 (1.8323-2.064)	1.9963 (1.88-2.1197)
Type of non-aspirin NSAIDs					
none	475 938 (79.79%)	120 544 (20.21%)	1 (reference)	1 (reference)	1 (reference)
diclofenac (local)	953 (69.01%)	428 (30.99%)	1.7446 (1.5563-1.9556)	1.319 (1.1681-1.4893)	1.3779 (1.2191-1.5573)
diclofenac (systemic)	17 563 (74.1%)	6 138 (25.9%)	1.3735 (1.3333-1.415)	1.3409 (1.3002-1.3829)	1.4611 (1.4164-1.5073)
naproxen (local)	(NA)	(NA)	NA	NA	NA
naproxen (systemic)	2 671 (68.28%)	1 241 (31.72%)	1.8101 (1.6918-1.9367)	1.7114 (1.595-1.8363)	1.7637 (1.6426-1.8937)
celecoxib	11 (100%)	(0%)	1.0579 (0.2951-3.792)	0.8692 (0.227-3.3277)	0.8823 (0.2342-3.3245)
ibuprofen (local)	(NA)	(NA)	3.879 (0.5464-27.5376)	2.7369 (0.3233-23.1674)	2.4843 (0.2576-23.9546)
ibuprofen (systemic)	110 (78.57%)	30 (21.43%)	1.0579 (0.7065-1.5841)	0.9642 (0.6324-1.4699)	1.1129 (0.7275-1.7025)

rofecoxib	(NA)	(NA)	0.0007 (0->1000)	0.0008 (0->1000)	0.0011 (0->1000)
indomethacin (local)	10 (100%)	(0%)	0.7758 (0.17-3.5407)	0.6761 (0.1377-3.3195)	0.8343 (0.172-4.0465)
indomethacin (systemic)	157 (67.38%)	76 (32.62%)	1.8782 (1.4281-2.4702)	1.6126 (1.2084-2.1522)	1.7677 (1.3211-2.3653)
Maternal age at index date					
15-19	20 953 (74.04%)	7 346 (25.96%)	2.0231 (1.9649-2.083)	2.011 (1.9531-2.0707)	1.9617 (1.9048-2.0203)
20-24	66 839 (80.85%)	15 833 (19.15%)	1.3669 (1.3384-1.3961)	1.362 (1.3335-1.3911)	1.3308 (1.3028-1.3594)
25-29	178 770 (85.23%)	30 980 (14.77%)	1 (reference)	1 (reference)	1 (reference)
30-34	167 744 (82%)	36 833 (18%)	1.2671 (1.2463-1.2882)	1.2649 (1.2441-1.286)	1.2207 (1.2005-1.2412)
35-39	54 329 (68.83%)	24 607 (31.17%)	2.6136 (2.5637-2.6645)	2.5995 (2.5497-2.6503)	2.5339 (2.485-2.5838)
40-45	7 569 (39.84%)	11 428 (60.16%)	8.7125 (8.4428-8.9909)	8.5863 (8.3198-8.8613)	8.4099 (8.1469-8.6815)

Table 15.S. Sensitivity analysis 4 of spontaneous abortions: replication of the published sensitivity analysis of the Rosa study (Amendment 1, binary exposure).

Variable	Controls N=394,327	Cases N=88,176	OR (95% CI)* crude	adjusted (1)	adjusted (2)
Type of gynecology anti-infectives					
none	365 217 (81.71%)	81 738 (18.29%)	1 (reference)	1 (reference)	1 (reference)
butoconazole	4 389 (81.78%)	978 (18.22%)	0.9965 (0.9294-1.0684)	0.9937 (0.9249-1.0675)	1.0412 (0.9689-1.1189)
miconazole (local)	10 565 (79.96%)	2 648 (20.04%)	1.1246 (1.077-1.1743)	0.9235 (0.7991-1.0674)	0.9509 (0.8214-1.1009)
miconazole (systemic)	(NA)	(NA)	NA	NA	NA
clotrimazole	12 166 (86.18%)	1 951 (13.82%)	0.7108 (0.6772-0.746)	0.7601 (0.7235-0.7985)	0.8128 (0.7735-0.8541)
nystatin (local)	(NA)	(NA)	NA	NA	NA
nystatin (systemic)	40 (74.07%)	14 (25.93%)	1.5653 (0.8516-2.877)	1.6634 (0.884-3.1301)	1.8581 (0.987-3.498)
metronidazole (local)	10 902 (79.73%)	2 772 (20.27%)	1.1415 (1.0942-1.1909)	1.1811 (1.0244-1.3619)	1.1849 (1.0259-1.3686)
metronidazole (systemic)	4 326 (75.07%)	1 437 (24.93%)	1.4936 (1.4064-1.5861)	1.5104 (1.4178-1.6092)	1.5296 (1.4353-1.6301)
Type of non-aspirin NSAIDs					
none	369 517 (81.81%)	82 155 (18.19%)	1 (reference)	1 (reference)	1 (reference)
diclofenac (local)	997 (72.99%)	369 (27.01%)	1.6579 (1.4709-1.8686)	1.3777 (1.2144-1.563)	1.4313 (1.2608-1.6249)
diclofenac (systemic)	20 813 (81.05%)	4 867 (18.95%)	1.0484 (1.0153-1.0826)	1.0268 (0.9933-1.0614)	1.095 (1.0591-1.1321)
naproxen (local)	(NA)	(NA)	NA	NA	NA
naproxen (systemic)	3 321 (76.7%)	1 009 (23.3%)	1.3629 (1.2697-1.4629)	1.3111 (1.2183-1.411)	1.3199 (1.2259-1.4212)
celecoxib	13 (100%)	(0%)	1.032 (0.2941-3.6216)	0.7804 (0.2117-2.876)	0.7743 (0.2118-2.8312)
ibuprofen (local)	(NA)	(NA)	8.9443 (0.811-98.6403)	5.3586 (0.3994-71.899)	4.4823 (0.2969-67.6788)
ibuprofen (systemic)	142 (86.06%)	23 (13.94%)	0.7243 (0.4662-1.1253)	0.7044 (0.4476-1.1087)	0.7874 (0.4994-1.2414)

rofecoxib	(NA)	(NA)	0.0009 (0->1000)	0.0011 (0->1000)	0.0013 (0->1000)
indomethacin (local)	(NA)	(NA)	0.4969 (0.063-3.9213)	0.377 (0.0435-3.2629)	0.4256 (0.0492-3.6845)
indomethacin (systemic)	190 (74.22%)	66 (25.78%)	1.5539 (1.1742-2.0562)	1.4145 (1.0565-1.8937)	1.5141 (1.13-2.0286)
Maternal age at index date					
15-19	15 870 (75.94%)	5 028 (24.06%)	2.1477 (2.0742-2.2238)	2.1406 (2.0672-2.2165)	2.0984 (2.0261-2.1733)
20-24	52 331 (82.94%)	10 763 (17.06%)	1.3942 (1.3594-1.4298)	1.3911 (1.3564-1.4267)	1.3702 (1.3358-1.4054)
25-29	144 475 (87.14%)	21 313 (12.86%)	1 (reference)	1 (reference)	1 (reference)
30-34	133 023 (83.92%)	25 485 (16.08%)	1.2987 (1.2734-1.3245)	1.2982 (1.273-1.324)	1.2562 (1.2316-1.2813)
35-39	42 413 (71.47%)	16 929 (28.53%)	2.7057 (2.6445-2.7684)	2.7012 (2.64-2.7638)	2.6101 (2.5506-2.671)
40-45	5 711 (42.01%)	7 884 (57.99%)	9.358 (9.0183-9.7104)	9.3099 (8.9717-9.6609)	9.095 (8.7626-9.44)

Table 15.T. Sensitivity analysis 5 of spontaneous abortions: cases and controls restricted to pregnancies with reported AFP screening test, drug exposure in the last 16 weeks before reported date of AFP screening test (Amendment 1, binary exposure).

Variable	Controls N=441,301	Cases N=5374	OR (95% CI)*		
			crude	adjusted (1)	adjusted (2)
Type of gynecology anti-infectives					
none	398 468 (98.78%)	4 905 (1.22%)	1 (reference)	1 (reference)	1 (reference)
butoconazole	3 438 (99.25%)	26 (0.75%)	0.6192 (0.4206-0.9115)	0.6367 (0.4323-0.9379)	0.6375 (0.4328-0.939)
miconazole (local)	16 215 (98.66%)	220 (1.34%)	1.119 (0.9769-1.2818)	1.222 (0.7645-1.9533)	1.2537 (0.7794-2.0164)
miconazole (systemic)	(NA)	(NA)	NA	NA	NA
clotrimazole	22 673 (99.04%)	219 (0.96%)	0.7844 (0.6847-0.8986)	0.8261 (0.7209-0.9467)	0.8675 (0.7566-0.9945)
nystatin (local)	(NA)	(NA)	NA	NA	NA
nystatin (systemic)	26 (100%)	(0%)	0.0003 (0->1000)	0.0003 (0->1000)	0.0004 (0->1000)
metronidazole (local)	17 034 (98.67%)	229 (1.33%)	1.1086 (0.9703-1.2666)	0.9428 (0.5931-1.4987)	0.9356 (0.5851-1.4962)
metronidazole (systemic)	3 051 (98.55%)	45 (1.45%)	1.213 (0.9026-1.6301)	1.236 (0.9121-1.675)	1.2701 (0.9372-1.7213)
Type of non-aspirin NSAIDs					
none	429 631 (98.8%)	5 208 (1.2%)	1 (reference)	1 (reference)	1 (reference)
diclofenac (local)	665 (97.94%)	14 (2.06%)	1.7307 (1.0187-2.9403)	1.4825 (0.8693-2.5285)	1.5519 (0.9097-2.6477)
diclofenac (systemic)	9 761 (98.64%)	135 (1.36%)	1.1392 (0.9592-1.3531)	1.1109 (0.9347-1.3202)	1.1773 (0.9904-1.3996)
naproxen (local)	(NA)	(NA)	NA	NA	NA
naproxen (systemic)	1 321 (98.44%)	21 (1.56%)	1.3066 (0.8483-2.0125)	1.2293 (0.7959-1.8986)	1.2385 (0.8017-1.9134)
celecoxib	(NA)	(NA)	0.0021 (0->1000)	0.0002 (0->1000)	0.0003 (0->1000)
ibuprofen (local)	(NA)	(NA)	NA	NA	NA
ibuprofen (systemic)	57 (100%)	(0%)	1.4407 (0.1995-10.4064)	1.4625 (0.2009-10.6485)	1.6167 (0.222-11.7707)

rofecoxib	(NA)	(NA)	0.0021 (0->1000)	0.0003 (0->1000)	0.0004 (0->1000)
indomethacin (local)	(NA)	(NA)	0.0008 (0->1000)	0.0003 (0->1000)	0.0003 (0->1000)
indomethacin (systemic)	93 (100%)	(0%)	0.883 (0.1231-6.3356)	0.804 (0.1114-5.7998)	0.8723 (0.1209-6.2922)
Maternal age at index date					
15-19	16 206 (98.32%)	277 (1.68%)	2.0536 (1.8028-2.3392)	2.0425 (1.7931-2.3267)	2.0336 (1.7852-2.3166)
20-24	58 546 (98.96%)	616 (1.04%)	1.2641 (1.1488-1.3911)	1.2615 (1.1464-1.3882)	1.2574 (1.1426-1.3836)
25-29	163 158 (99.17%)	1 358 (0.83%)	1 (reference)	1 (reference)	1 (reference)
30-34	151 745 (98.86%)	1 748 (1.14%)	1.384 (1.2888-1.4862)	1.3837 (1.2886-1.4859)	1.3468 (1.254-1.4466)
35-39	45 408 (97.69%)	1 075 (2.31%)	2.8444 (2.6239-3.0834)	2.8391 (2.6189-3.0779)	2.7572 (2.5427-2.9897)
40-45	5 854 (95.39%)	283 (4.61%)	5.8082 (5.0966-6.6192)	5.7713 (5.0637-6.5778)	5.5933 (4.9061-6.3766)

Table 15.U. Sensitivity analysis 6 of spontaneous abortions: cases also include pregnancies without identified pregnancy outcome (Amendment 1, binary exposure).

Variable	Controls N=493,112	Cases N=290,179	OR (95% CI)*		
			crude	adjusted (1)	adjusted (2)
Type of gynecology anti-infectives					
none	454 425 (62.94%)	267 573 (37.06%)	1 (reference)	1 (reference)	1 (reference)
butoconazole	4 553 (58.07%)	3 287 (41.93%)	1.2294 (1.1752-1.2861)	1.2858 (1.2263-1.3483)	1.3654 (1.302-1.432)
miconazole (local)	14 056 (60.27%)	9 264 (39.73%)	1.124 (1.0944-1.1543)	0.7412 (0.6787-0.8094)	0.7628 (0.6982-0.8334)
miconazole (systemic)	(NA)	(NA)	NA	NA	NA
clotrimazole	18 663 (74.46%)	6 402 (25.54%)	0.5735 (0.5573-0.5903)	0.6097 (0.5916-0.6284)	0.6483 (0.629-0.6683)
nystatin (local)	(NA)	(NA)	NA	NA	NA
nystatin (systemic)	36 (46.75%)	41 (53.25%)	1.9355 (1.237-3.0284)	1.996 (1.2427-3.206)	2.1954 (1.3654-3.5302)
metronidazole (local)	14 618 (59.34%)	10 017 (40.66%)	1.1704 (1.1405-1.201)	1.462 (1.3418-1.593)	1.4683 (1.3469-1.6006)
metronidazole (systemic)	3 889 (40.69%)	5 669 (59.31%)	2.5066 (2.4057-2.6116)	2.3003 (2.2006-2.4046)	2.3414 (2.2394-2.4479)
Type of non-aspirin NSAIDs					
none	472 357 (64.05%)	265 148 (35.95%)	1 (reference)	1 (reference)	1 (reference)
diclofenac (local)	942 (32.11%)	1 992 (67.89%)	3.6114 (3.3417-3.903)	1.6811 (1.5368-1.839)	1.7308 (1.5815-1.8941)
diclofenac (systemic)	17 385 (47.16%)	19 479 (52.84%)	1.9691 (1.9282-2.0108)	1.6947 (1.6566-1.7337)	1.7987 (1.758-1.8403)
naproxen (local)	(NA)	(NA)	NA	NA	NA
naproxen (systemic)	2 641 (34.8%)	4 948 (65.2%)	3.2216 (3.0723-3.3782)	2.5678 (2.4403-2.702)	2.6168 (2.4862-2.7543)
celecoxib	10 (22.22%)	35 (77.78%)	5.9483 (2.9456-12.0119)	2.9459 (1.3307-6.5216)	2.7805 (1.2575-6.148)
ibuprofen (local)	(NA)	(NA)	3.3987 (0.6225-18.5558)	2.1394 (0.3213-14.2427)	1.8146 (0.2607-12.6303)
ibuprofen (systemic)	108 (54.27%)	91 (45.73%)	1.432 (1.0834-1.8927)	1.1035 (0.8106-1.5023)	1.2208 (0.8963-1.6627)

rofecoxib	(NA)	(NA)	0.0009 (0->1000)	0.001 (0->1000)	0.0013 (0->1000)
indomethacin (local)	10 (100%)	(0%)	1.5294 (0.6215-3.7638)	0.9872 (0.33-2.953)	1.1452 (0.3811-3.4412)
indomethacin (systemic)	155 (32.02%)	329 (67.98%)	3.6099 (2.9823-4.3697)	2.3895 (1.9349-2.951)	2.5696 (2.0793-3.1755)
Maternal age at index date					
15-19	20 629 (50.38%)	20 316 (49.62%)	2.7358 (2.6779-2.7949)	2.7349 (2.6768-2.7943)	2.7183 (2.6603-2.7776)
20-24	66 199 (63.19%)	38 560 (36.81%)	1.6181 (1.5933-1.6433)	1.6143 (1.5893-1.6395)	1.5967 (1.572-1.6218)
25-29	177 749 (73.53%)	63 986 (26.47%)	1 (reference)	1 (reference)	1 (reference)
30-34	166 639 (69.45%)	73 312 (30.55%)	1.2221 (1.2069-1.2376)	1.223 (1.2077-1.2385)	1.1914 (1.1764-1.2066)
35-39	53 774 (53.43%)	46 867 (46.57%)	2.4211 (2.3843-2.4585)	2.4083 (2.3715-2.4457)	2.3588 (2.3226-2.3956)
40-45	7 434 (22.52%)	25 578 (77.48%)	9.558 (9.3-9.8231)	9.3052 (9.0531-9.5644)	9.2633 (9.0115-9.5222)

15.3. Detailed results on congenital anomalies

15.3.1. Nervous system (EUROCAT al2)

The EUROCAT al2 code group has been defined as any reported ICD code in the Q00, Q01, Q02, Q03, Q04, Q05, Q06, Q07 code groups.

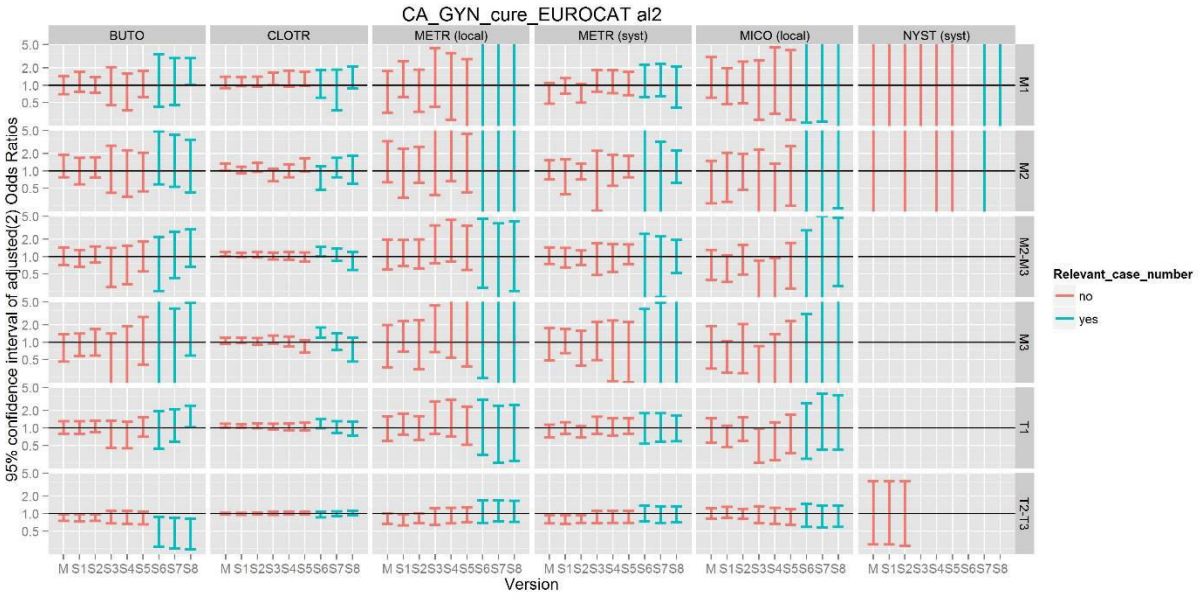
	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	9487	19.22 *
Excluding single outpatient reports (S3-S5)	3003	6.08 *
Excluding all outpatient reports (S6-S8)	1268	2.57 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		1.36 **

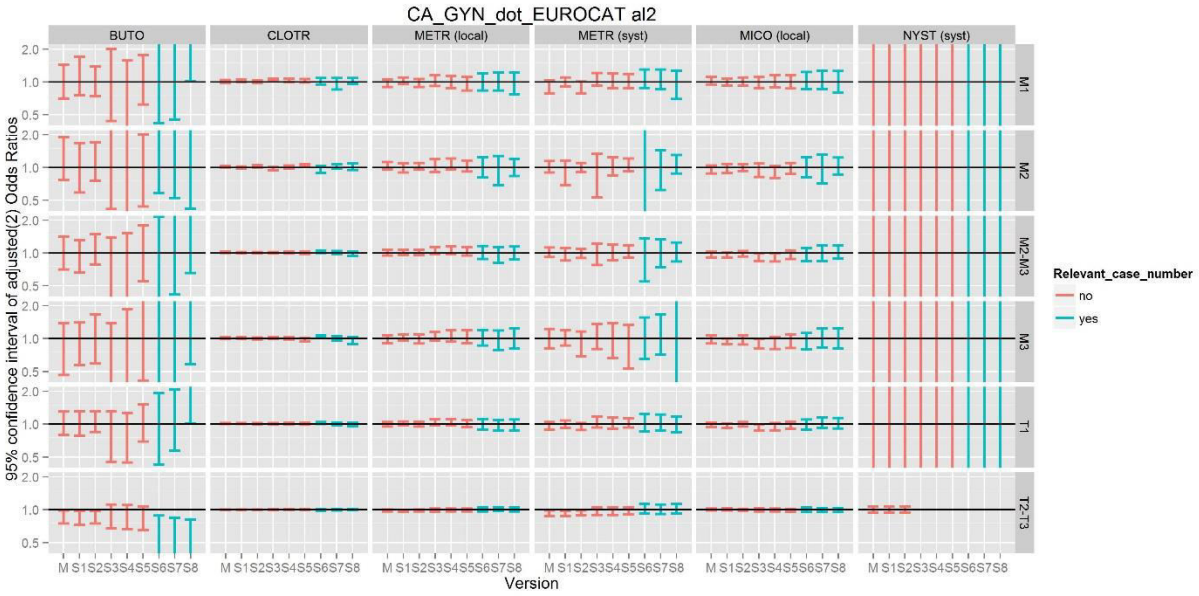
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

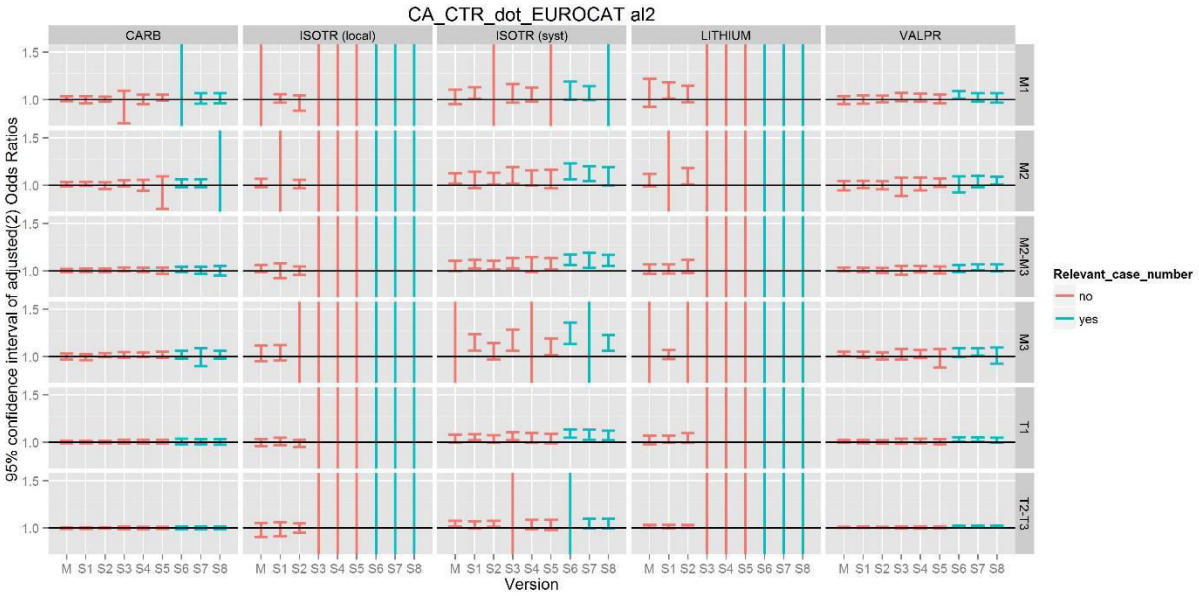
Based on the above numbers, outpatient reports may be unreliable for the analysis of congenital anomalies of the nervous system; hence, sensitivity analyses **S6-S8 are the most relevant ones** for the analysis of this code group.

Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.A. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.A. 95% confidence intervals of odds ratios of drug exposure in the al2 congenital anomaly group, adjusted to all confounders.
Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_EUROCAT al2
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
no
yes


CA_CTR_dot_EUROCAT al2
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
no
yes

15.3.2. Eye (EUROCAT al10)

The EUROCAT al10 code group has been defined as any reported ICD code in the Q10-Q15 code groups.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	970	1.97 *
Excluding single outpatient reports (S3-S5)	348	0.71 *
Excluding all outpatient reports (S6-S8)	238	0.48 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		0.66 **

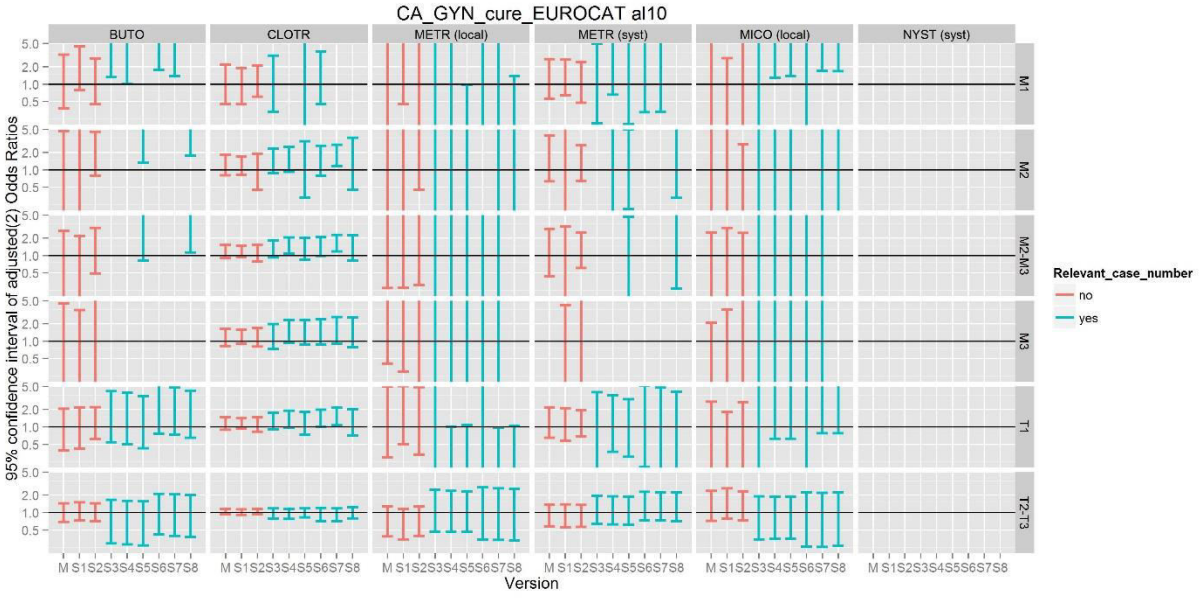
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

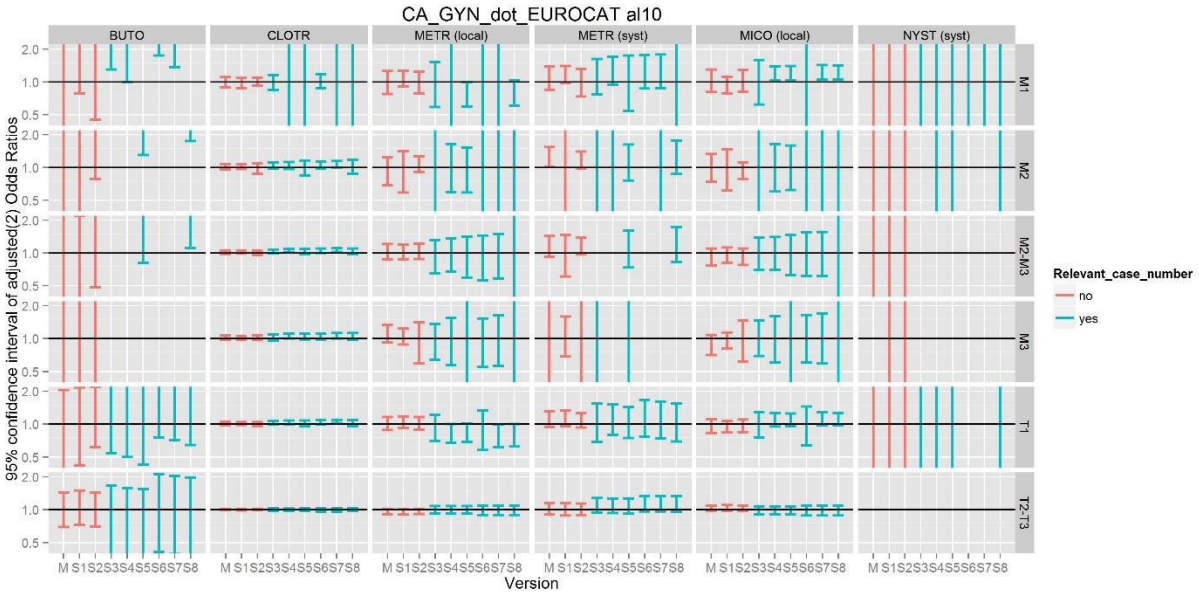
Based on the above numbers, single outpatient reports my be unreliable for the analysis of congenital anomalies of the eye; hence, sensitivity analyses S3-S8 are the most relevant ones for the analysis of this code group.

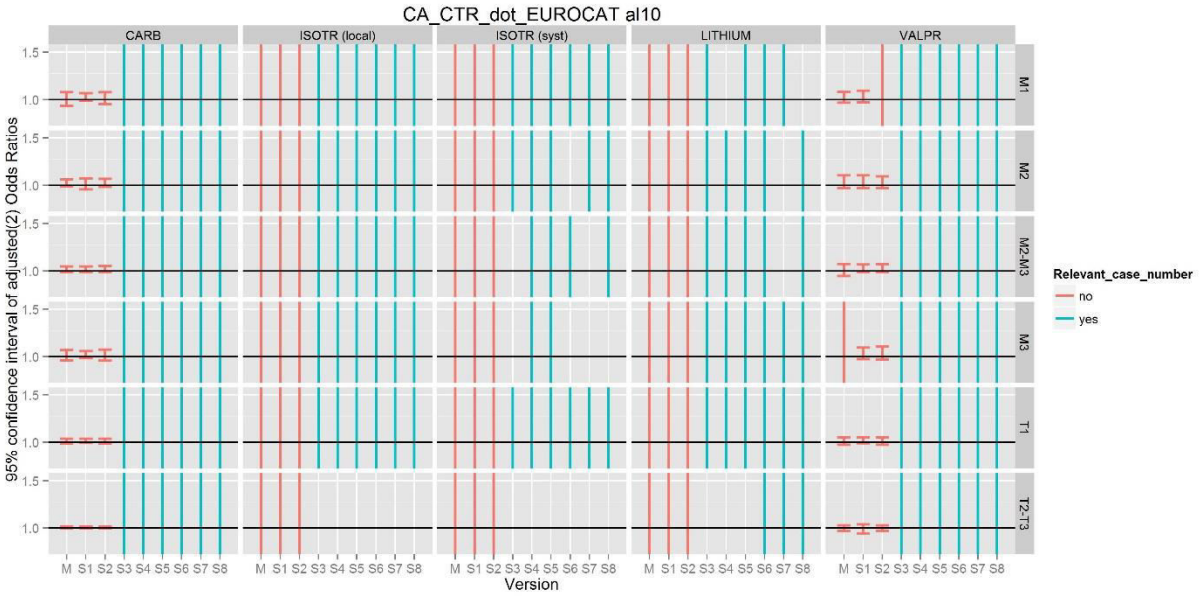
Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.B. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.B. 95% confidence intervals of odds ratios of drug exposure in the al10 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_EUROCAT al10
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
no
yes


CA_CTR_dot_EUROCAT al10
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
no
yes

15.3.3. Ear, face and neck (EUROCAT al15)

The EUROCAT al15 code group has been defined as any reported ICD code in the Q16-Q18 code groups.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	754	1.53 *
Excluding single outpatient reports (S3-S5)	605	1.23 *
Excluding all outpatient reports (S6-S8)	587	1.19 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		1.09 **

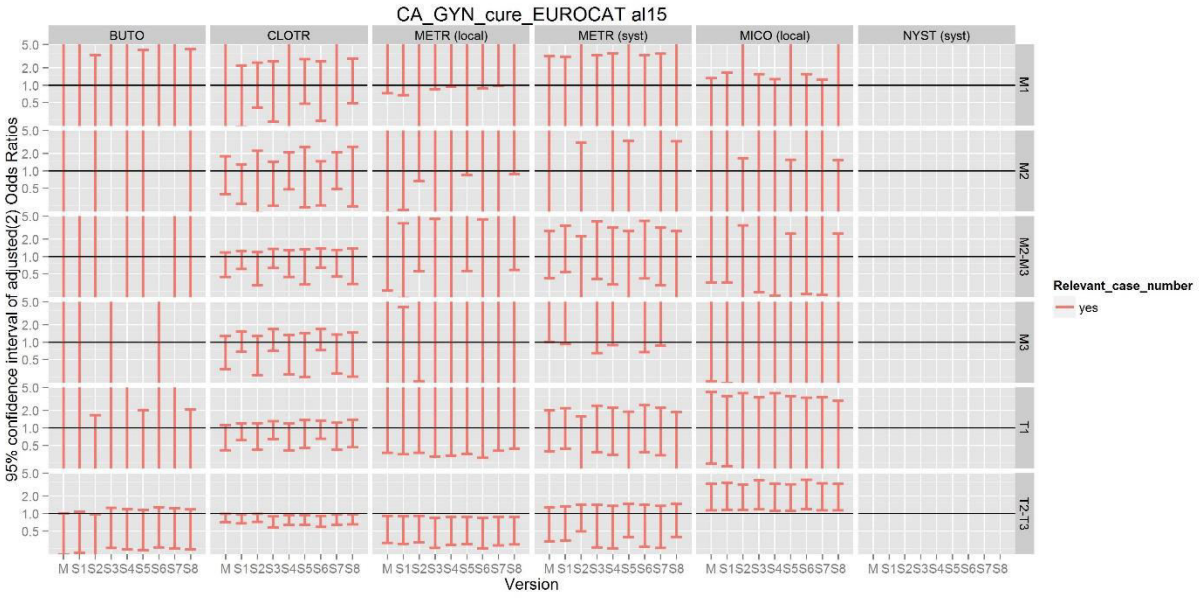
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

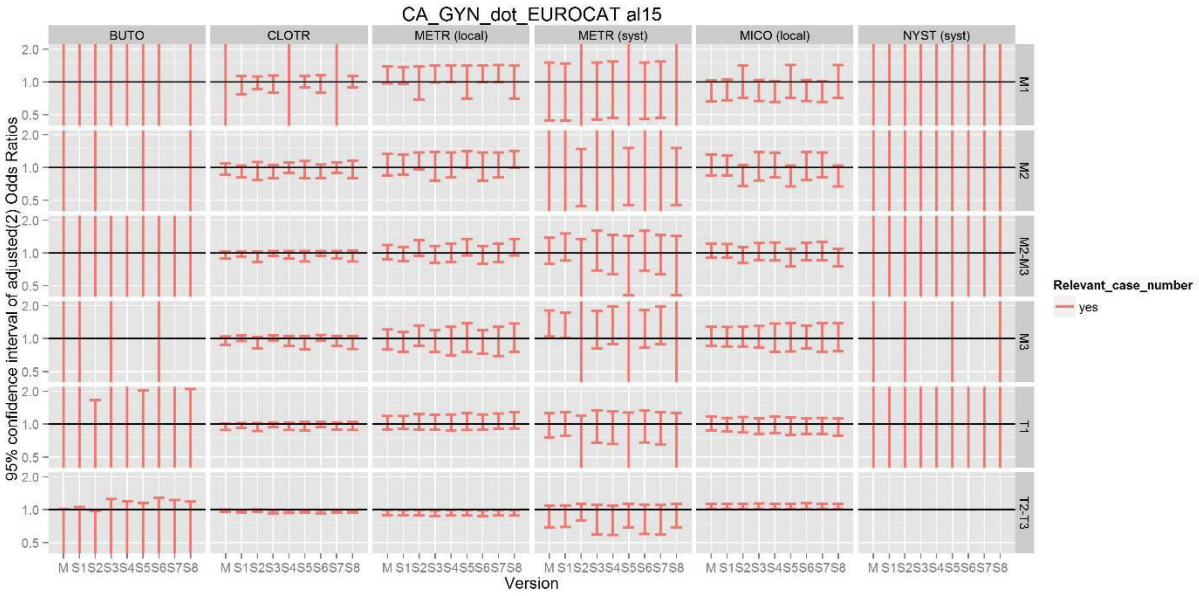
Based on the above numbers, the exclusion of single or all outpatient reports did not meaningfully reduce the number of al15 cases in the study. The observed rate is consistent with the national statistics (assuming some underreporting of outpatient cases to the registry). Acordingly, the main and sensitivity analyses have similar relevance for the analysis of this code group.

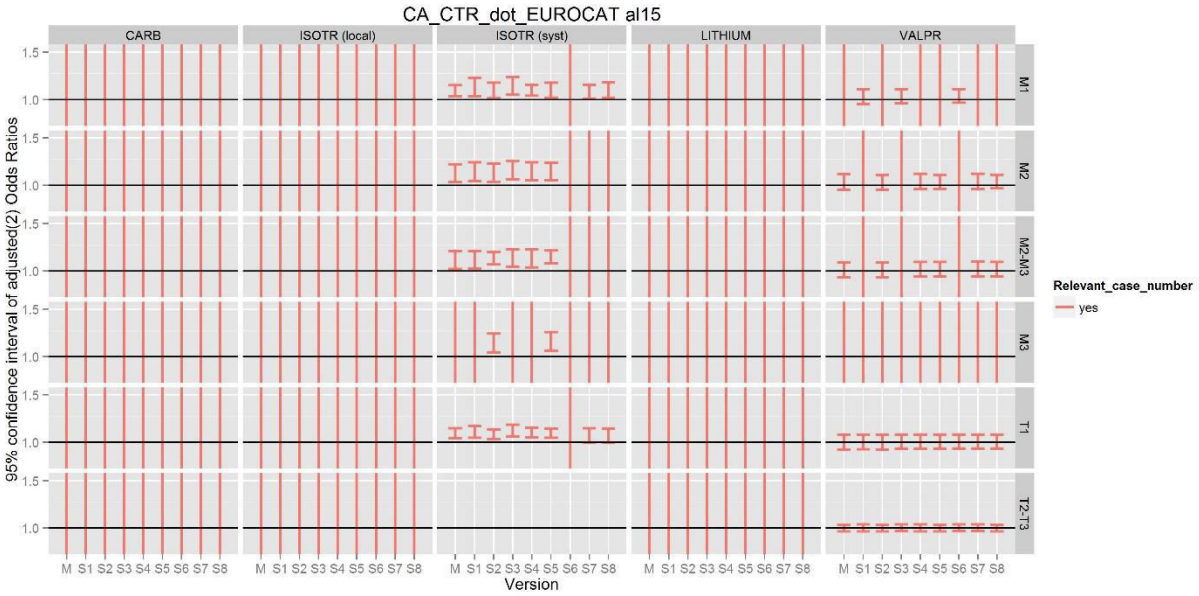
Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.C. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.C. 95% confidence intervals of odds ratios of drug exposure in the al15 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_EUROCAT al15
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
M S1S2S3S4S5S6S7S8
Version
Relevant_case_number
yes


CA_CTR_dot_EUROCAT al15
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
M S1 S2 S3 S4 S5 S6 S7 S8
Version
Relevant_case_number
yes

15.3.4. Congenital heart defects (EUROCAT al17)

The EUROCAT al17 code group has been defined as any reported ICD code in the Q20-Q26 code groups.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	20,102	40.73 *
Excluding single outpatient reports (S3-S5)	11,329	22.95 *
Excluding all outpatient reports (S6-S8)	9055	18.35 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		10.79 **

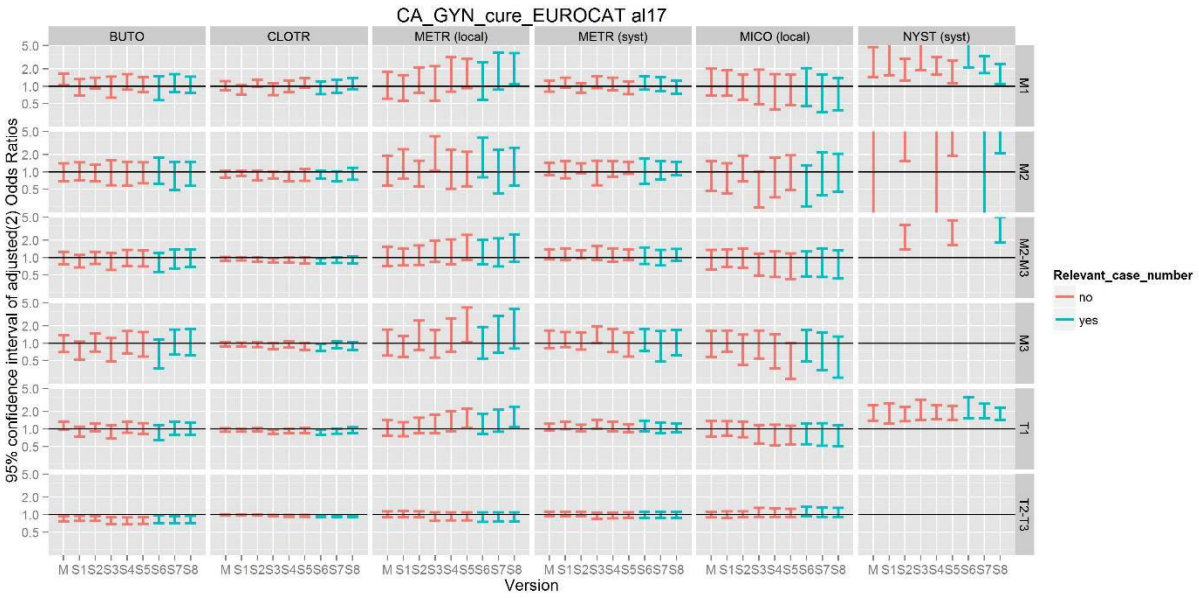
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

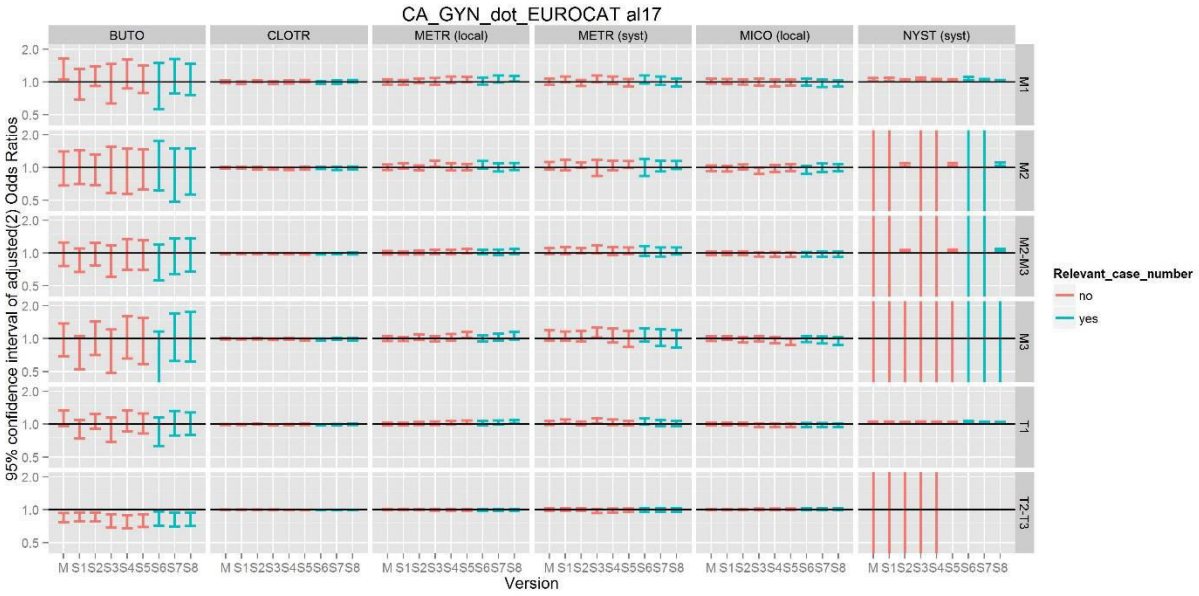
Based on the above numbers, outpatient reports may be unreliable for the analysis of congenital anomalies of congenital heart defects; hence, sensitivity analyses S6-S8 are the most relevant ones for the analysis of this code group.

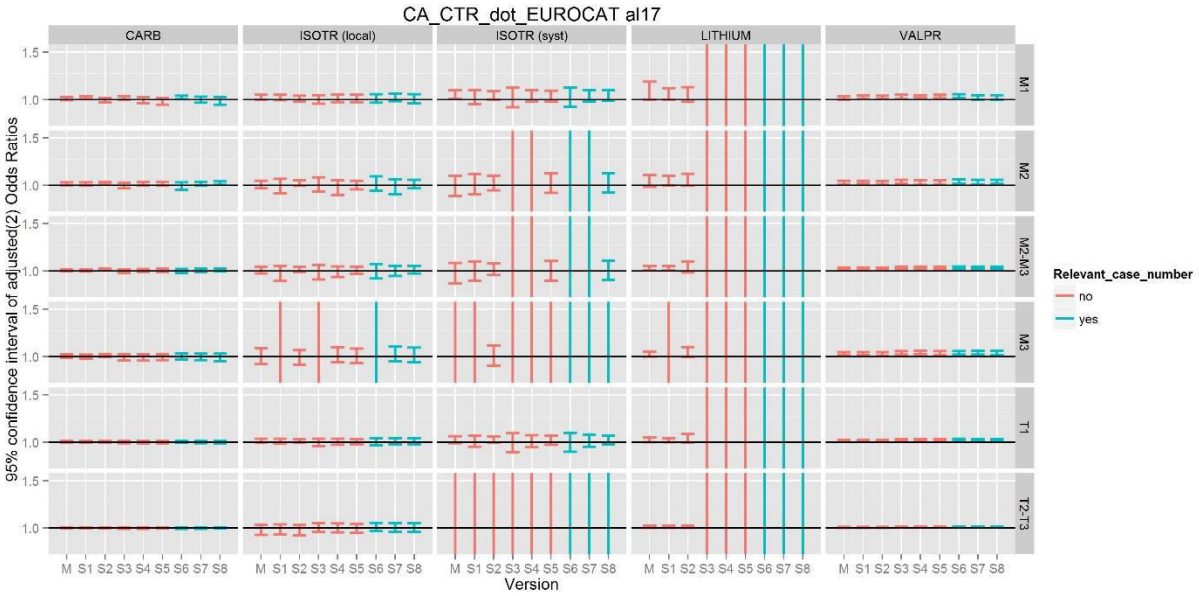
Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.D. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.D. 95% confidence intervals of odds ratios of drug exposure in the al17 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_EUROCAT al17
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
no
yes


CA_CTR_dot_EUROCAT al17
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
Version
Relevant_case_number
no
yes

15.3.5. Severe congenital heart defects (EUROCAT al97)

The EUROCAT al97 code group has been defined as any reported ICD code in the Q200, Q203, Q204, Q212, Q213, Q220, Q224, Q225, Q226, Q230, Q234, Q251, Q262 range.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	1503	3.05 *
Excluding single outpatient reports (S3-S5)	1234	2.50 *
Excluding all outpatient reports (S6-S8)	1089	2.21 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		1.39 **

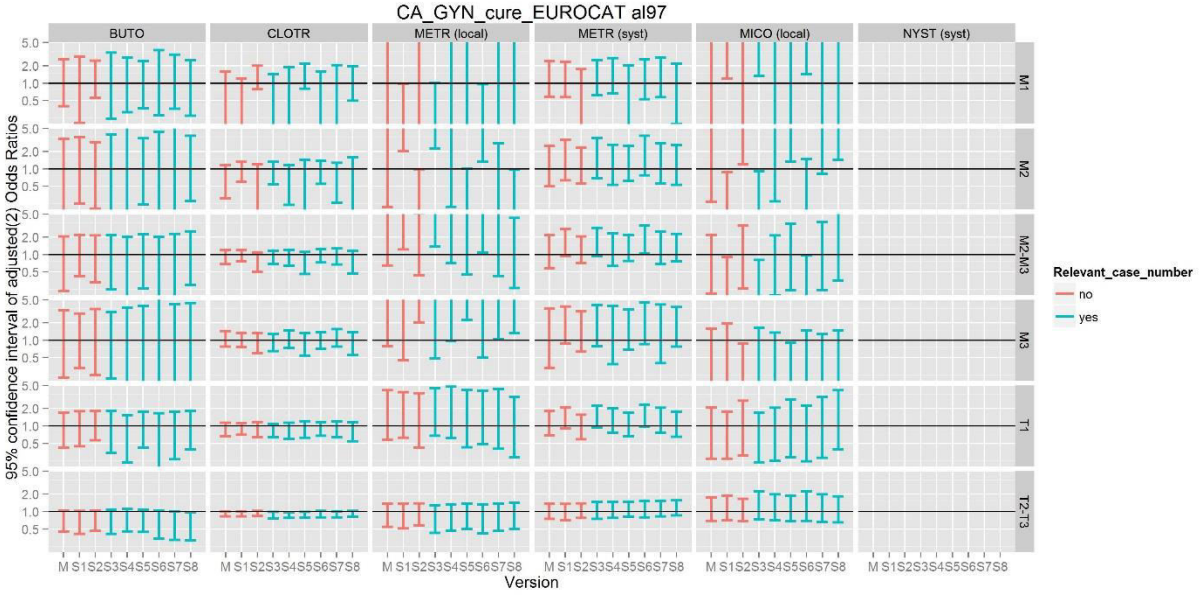
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

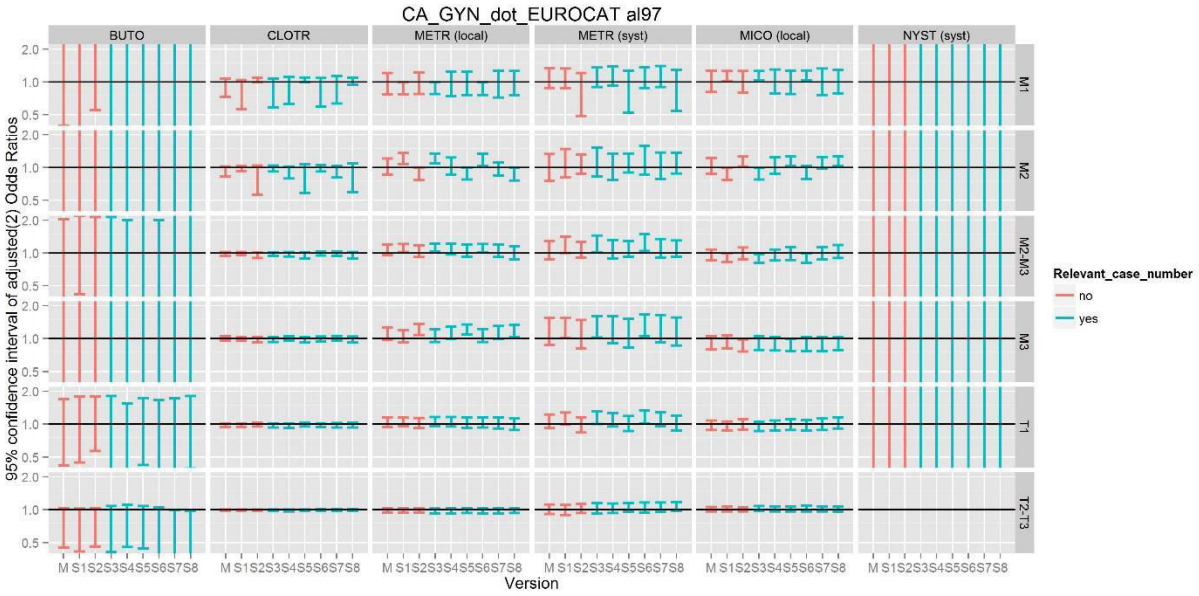
Based on the above numbers, single outpatient reports may be unreliable for the analysis of congenital anomalies of severe congenital heart defects; hence, sensitivity analyses S3-S8 are the most relevant ones for the analysis of this code group.

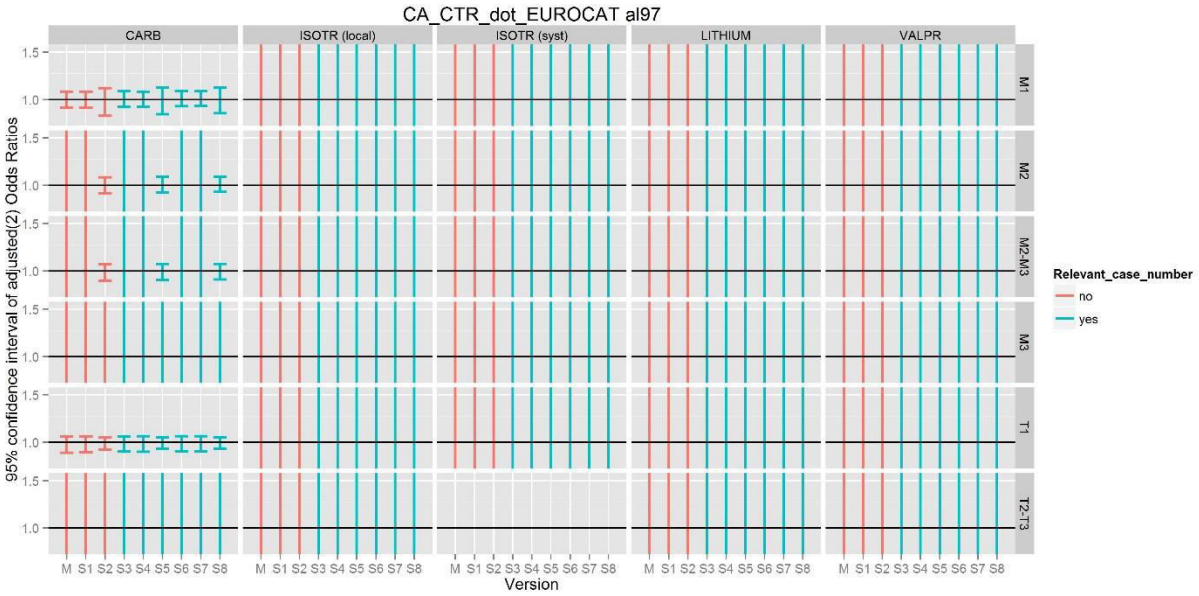
Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.3.5.A. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.E. 95% confidence intervals of odds ratios of drug exposure in the al97 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_EUROCAT al97
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
M S1S2S3S4S5S6S7S8
Version
Relevant_case_number
no
yes


CA_CTR_dot_EUROCAT al97
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
M S1 S2 S3 S4 S5 S6 S7 S8
Version
Relevant_case_number
no
yes

15.3.6. Ventricular septum defect (EUROCAT al21)

The EUROCAT al21 code group has been defined as any reported ICD code in the Q210 range.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	4301	8.71 *
Excluding single outpatient reports (S3-S5)	2472	5.01 *
Excluding all outpatient reports (S6-S8)	2014	4.08 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		2.06 **

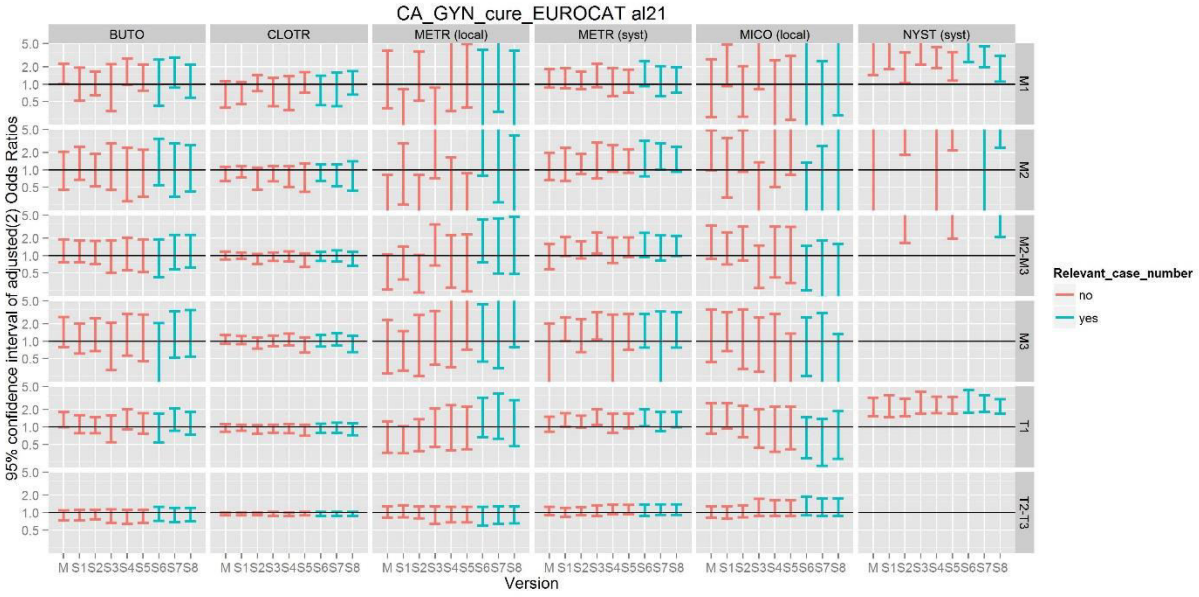
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

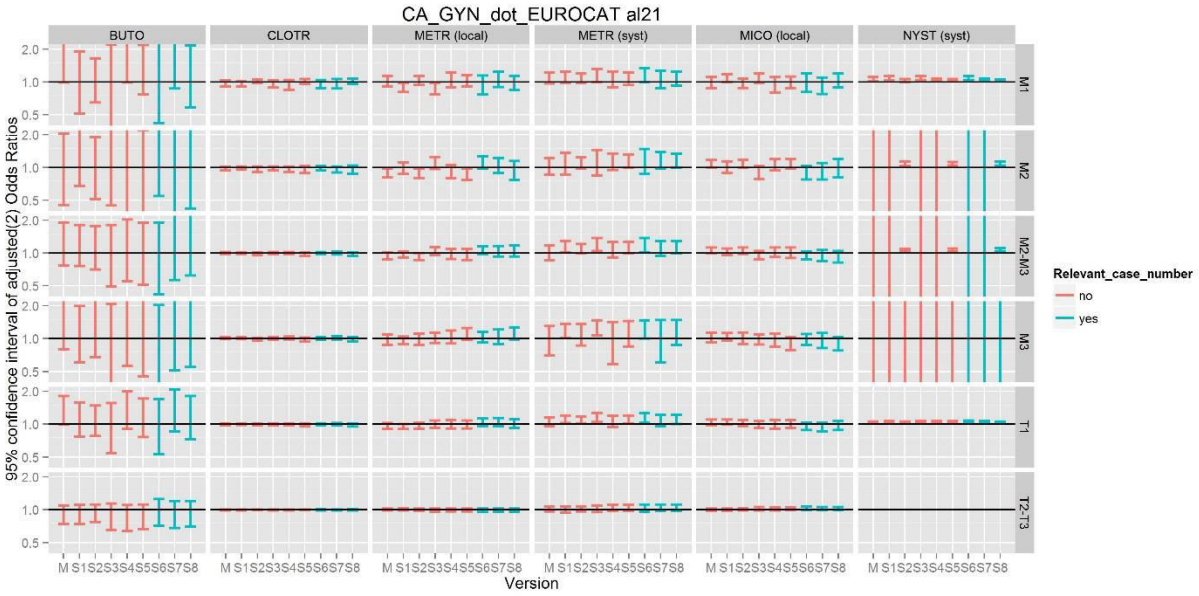
Based on the above numbers, single outpatient reports may be unreliable for the analysis of ventricular septum defects; hence, sensitivity analyses S6-S8 are the most relevant ones for the analysis of this code group.

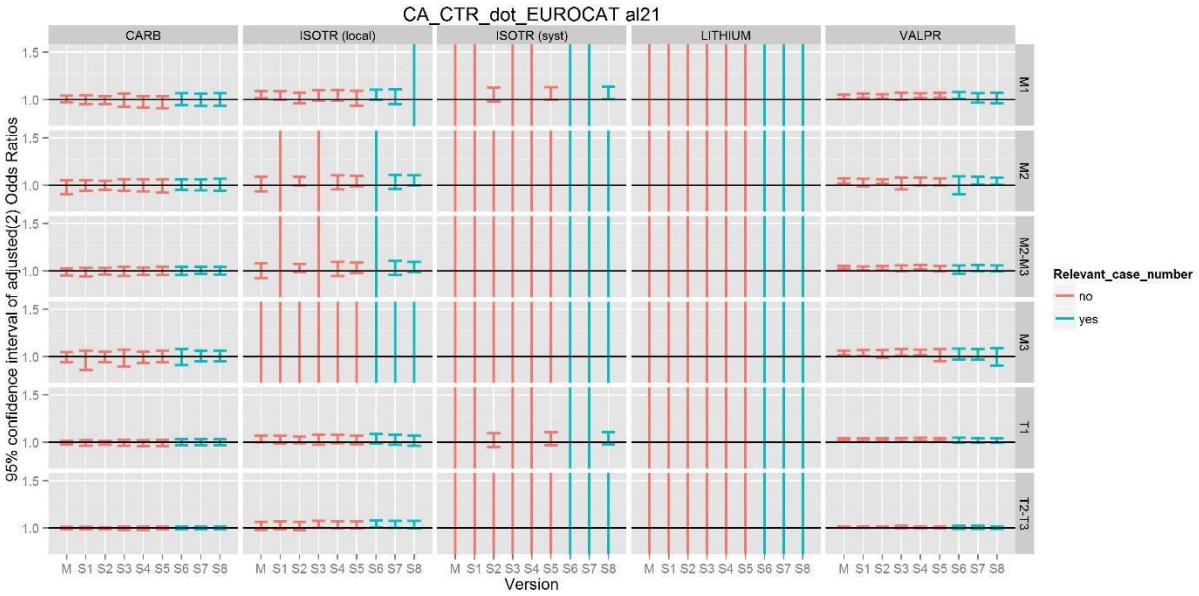
Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.F. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.F. 95% confidence intervals of odds ratios of drug exposure in the al21 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_EUROCAT al21
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
M S1S2S3S4S5S6S7S8
Version
Relevant_case_number
no
yes


CA_CTR_dot_EUROCAT al21
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
M S1 S2 S3 S4 S5 S6 S7 S8
Version
Relevant_case_number
no
yes

15.3.7. Atrial septum defect (EUROCAT al22)

The EUROCAT al22 code group has been defined as any reported ICD code in the Q211 range.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	13,922	28.21 *
Excluding single outpatient reports (S3-S5)	6814	13.81 *
Excluding all outpatient reports (S6-S8)	5091	10.32 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		3.68 **

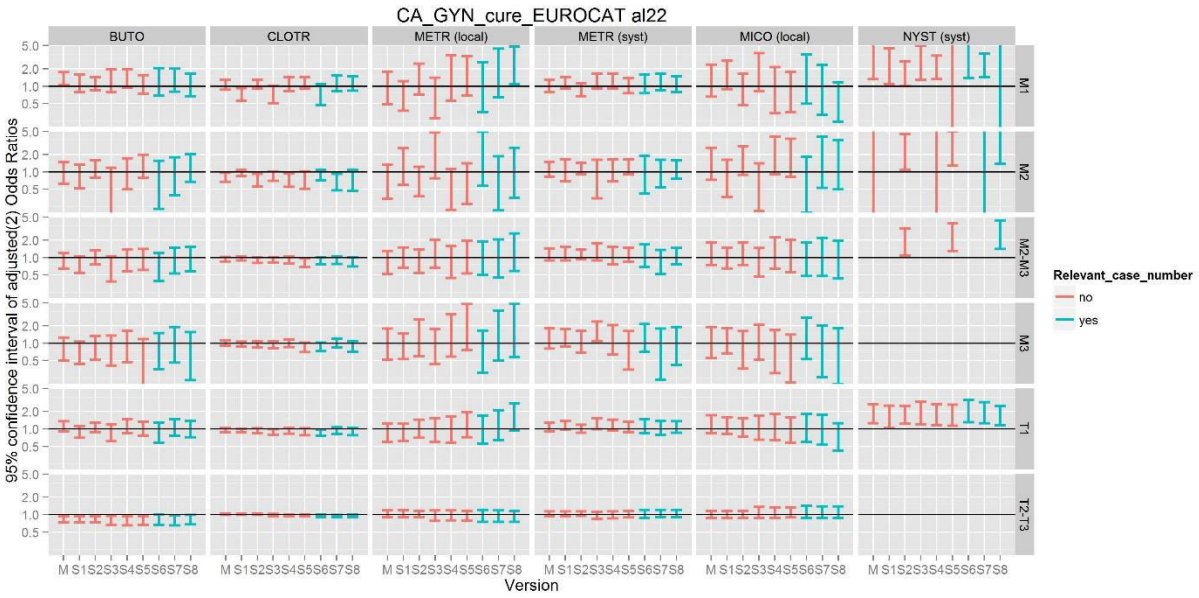
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

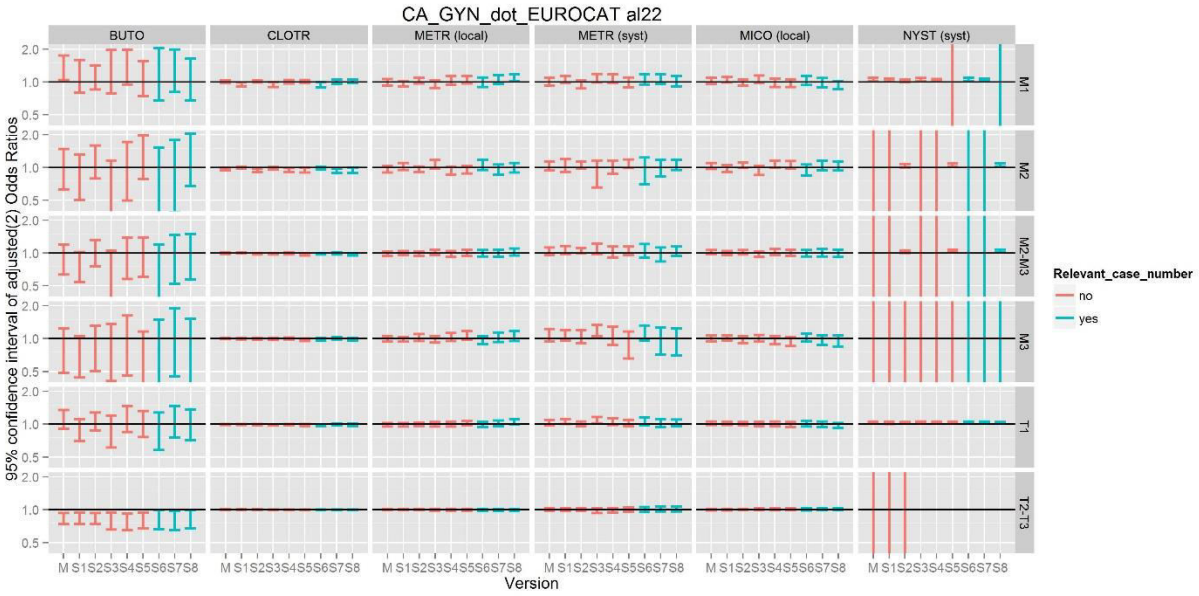
Based on the above numbers, outpatient reports may be unreliable for the analysis of atrial septum defects; hence, sensitivity analyses S6-S8 are the most relevant ones for the analysis of this code group. Assuming that inpatient OEP claims of atrial septum defect are reliable, under-reporting of atrial septum defects to the national registry may be substantial.

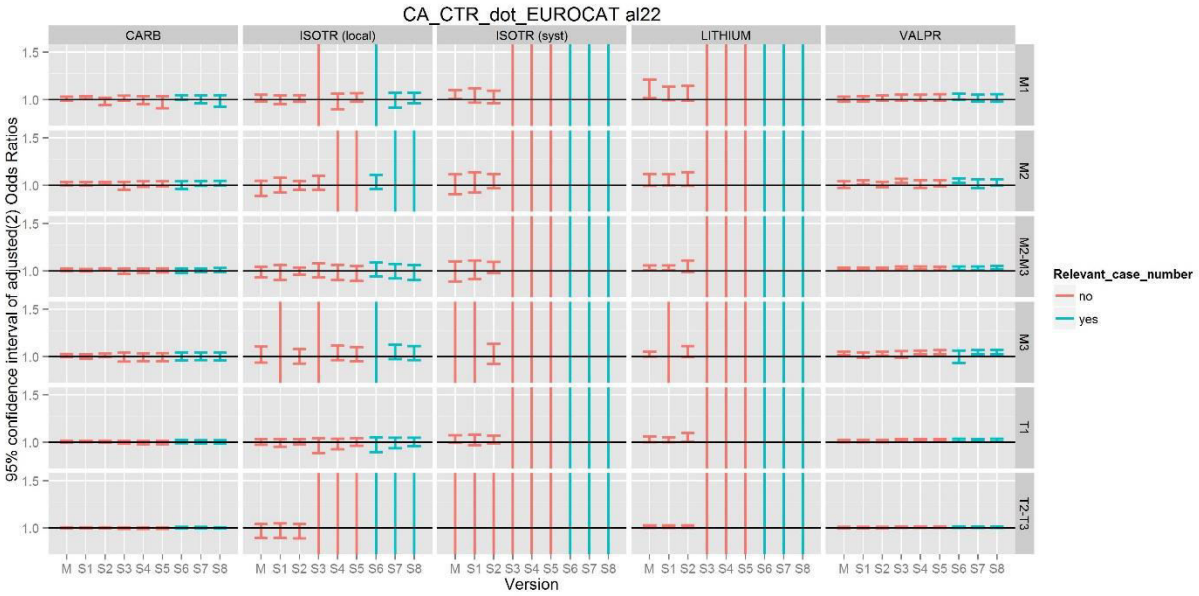
Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.G. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.G. 95% confidence intervals of odds ratios of drug exposure in the al22 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_EUROCAT al22
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
M S1 S2 S3 S4 S5 S6 S7 S8
Version
Relevant_case_number
no
yes


CA_CTR_dot_EUROCAT al22
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
M S1 S2 S3 S4 S5 S6 S7 S8
Version
Relevant_case_number
no
yes

15.3.8. Persistent Ductus arteriosus Botalli as only congenital heart defect in infants (EUROCAT al100)

For the EUROCAT al100 code group analysis, cases has been defined as live births with >37 weeks gestational age AND with a Q250 ICD code in their first year after birth, AND without any other congenital heart defect anomaly codes (as listed in EUROCAT group al17) during pregnancy or until the age of 1 year.

We could not identify any case belonging to the al100 group. Accordingly, this anomaly can not be investigated in this study.

The 2011 Annual Report of the Hungarian Congenital Abnormality Registry neither reported data on persistent ductus arteriosus Botalli as only congenital heart defect in infants.

15.3.9. Congenital heart defects, other (Custom RG01)

The custom RG01 code group has been defined as any reported al17 code not belonging to al21, al22, al97, al100.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	3975	8.05 *
Excluding single outpatient reports (S3-S5)	2488	5.04 *
Excluding all outpatient reports (S6-S8)	2119	4.29 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		3.64 **

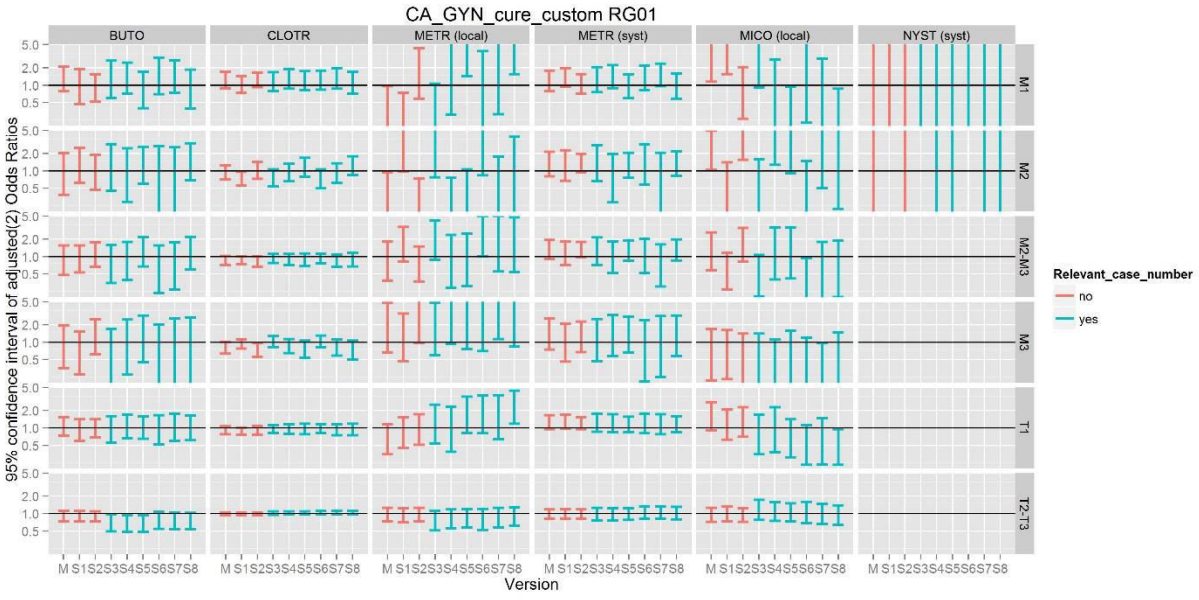
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

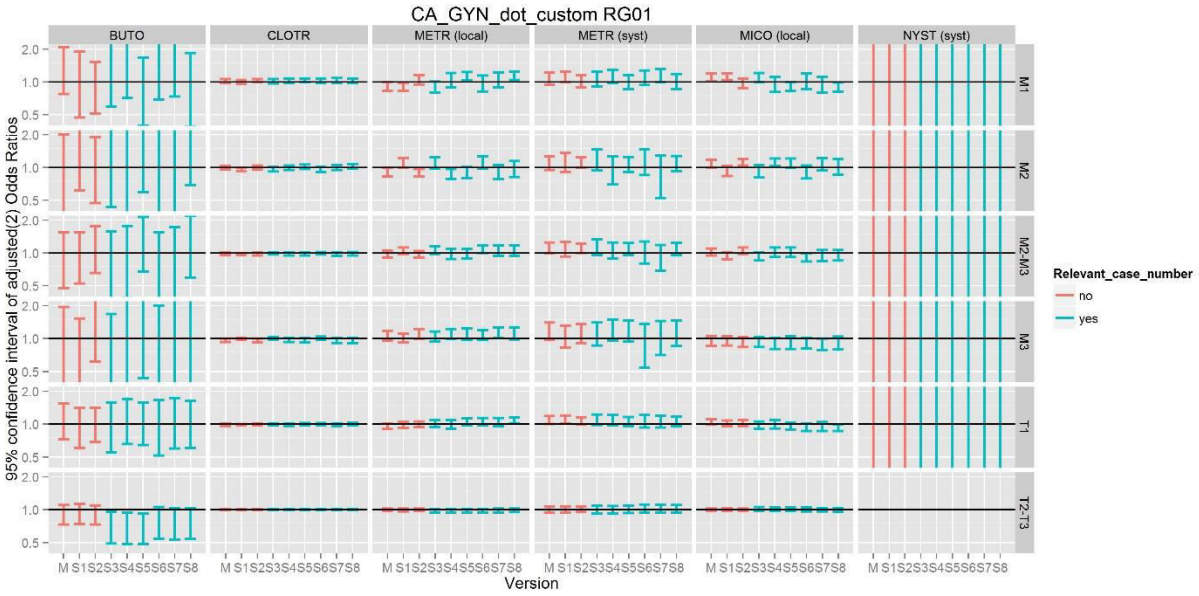
Based on the above numbers, single outpatient reports may be unreliable for the analysis of this group of heart defects; hence, sensitivity analyses S3-S8 are the most relevant ones for the analysis of this code group.

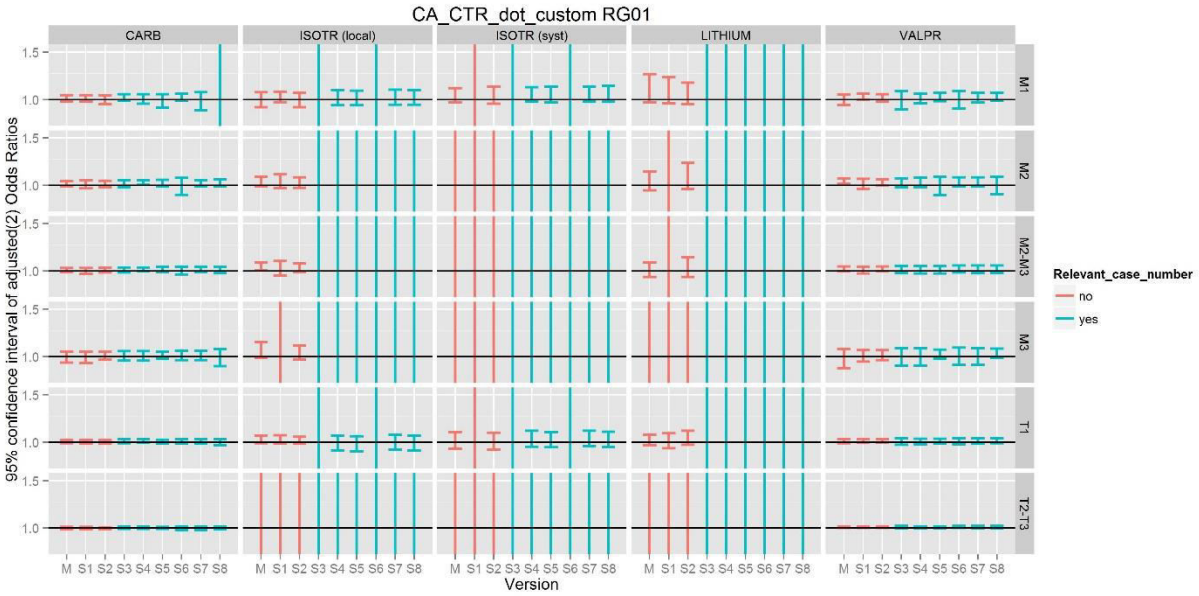
Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.H. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.H. 95% confidence intervals of odds ratios of drug exposure in the RG01 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_custom RG01
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
M S1 S2 S3 S4 S5 S6 S7 S8
Version
Relevant_case_number
no
yes


CA_CTR_dot_custom RG01
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
M S1 S2 S3 S4 S5 S6 S7 S8
Version
Relevant_case_number
no
yes

15.3.10. Respiratory (EUROCAT al34)

The EUROCAT al34 code group has been defined as any reported ICD code in the Q30-Q34 range.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	1617	3.28 *
Excluding single outpatient reports (S3-S5)	1072	2.17 *
Excluding all outpatient reports (S6-S8)	1023	2.07 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		0.53 **

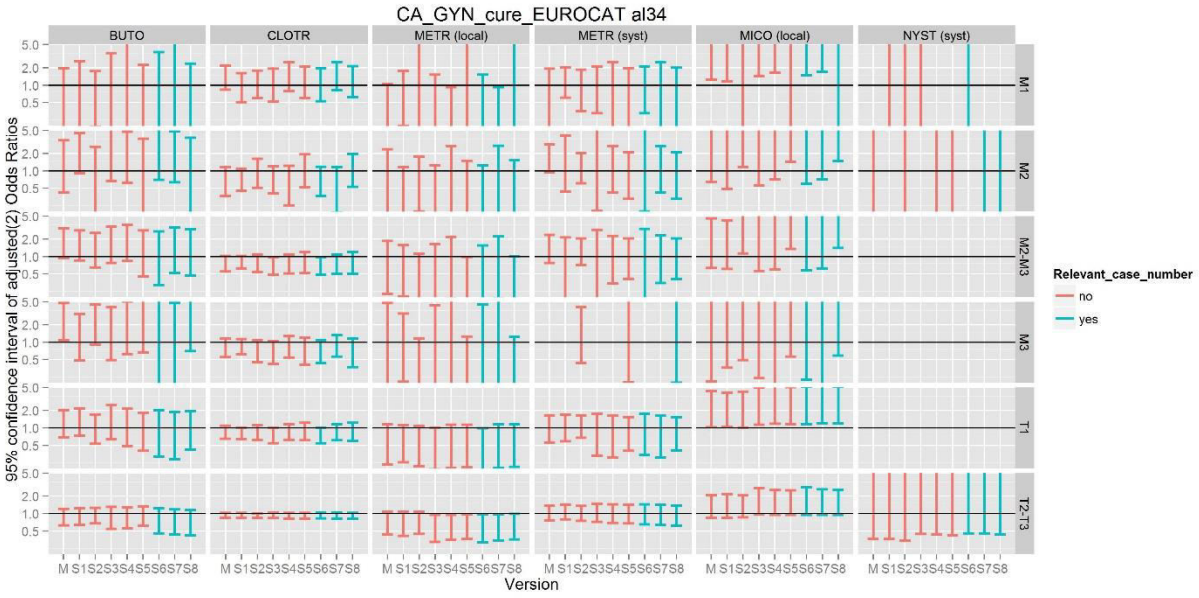
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

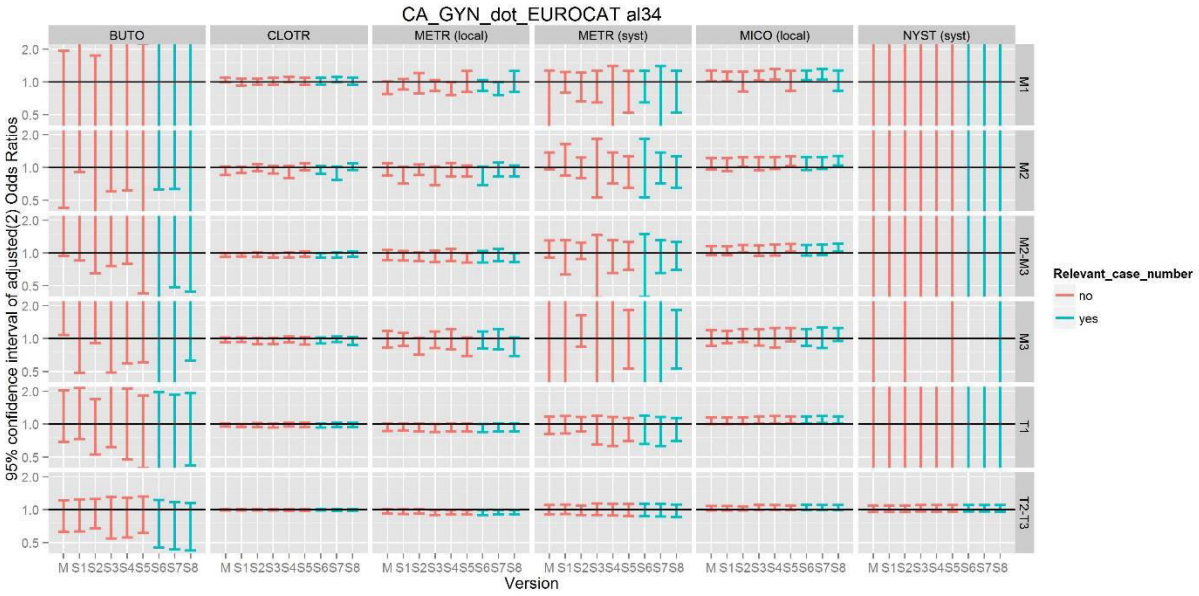
Based on the above numbers, outpatient reports may be unreliable for the analysis of congenital respiratory anomalies; hence, sensitivity analyses S6-S8 are the most relevant ones for the analysis of this code group. Assuming that inpatient OEP claims of respiratory anomalies are reliable, under-reporting of these anomalies to the national registry may be substantial.

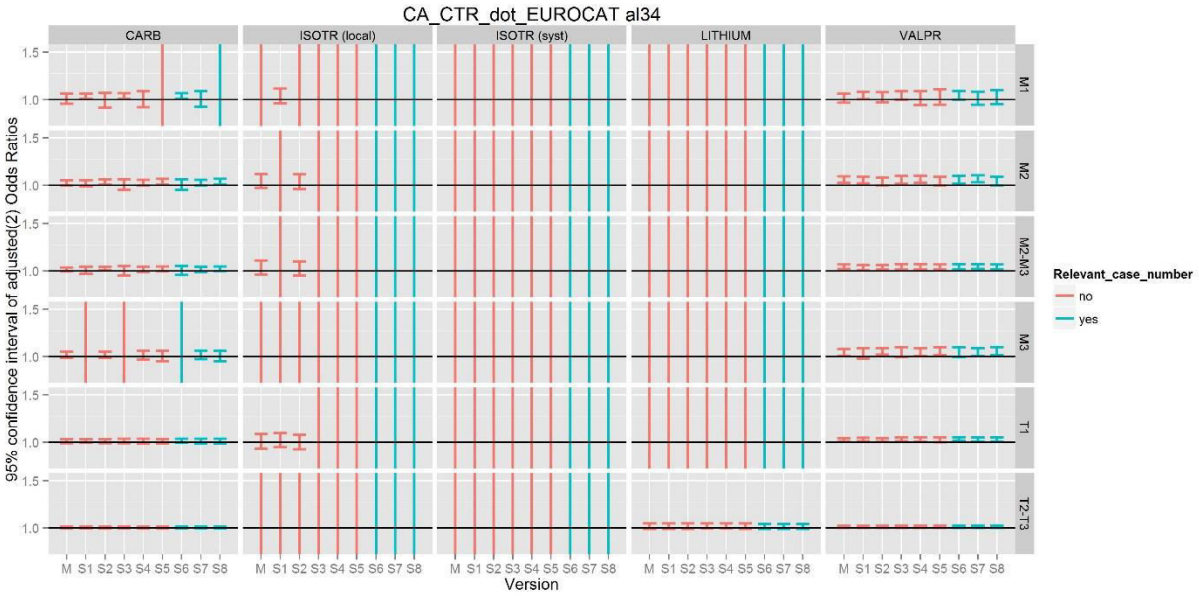
Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.I. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.I. 95% confidence intervals of odds ratios of drug exposure in the al34 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_EUROCAT al34
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
M S1S2S3S4S5S6S7S8
Version
Relevant_case_number
no
yes


CA_CTR_dot_EUROCAT al34
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
M S1 S2 S3 S4 S5 S6 S7 S8
Version
Relevant_case_number
no
yes

15.3.11. Oro-facial clefts (EUROCAT al101)

The EUROCAT al101 code group has been defined as any reported ICD code in the Q35-Q37 range.

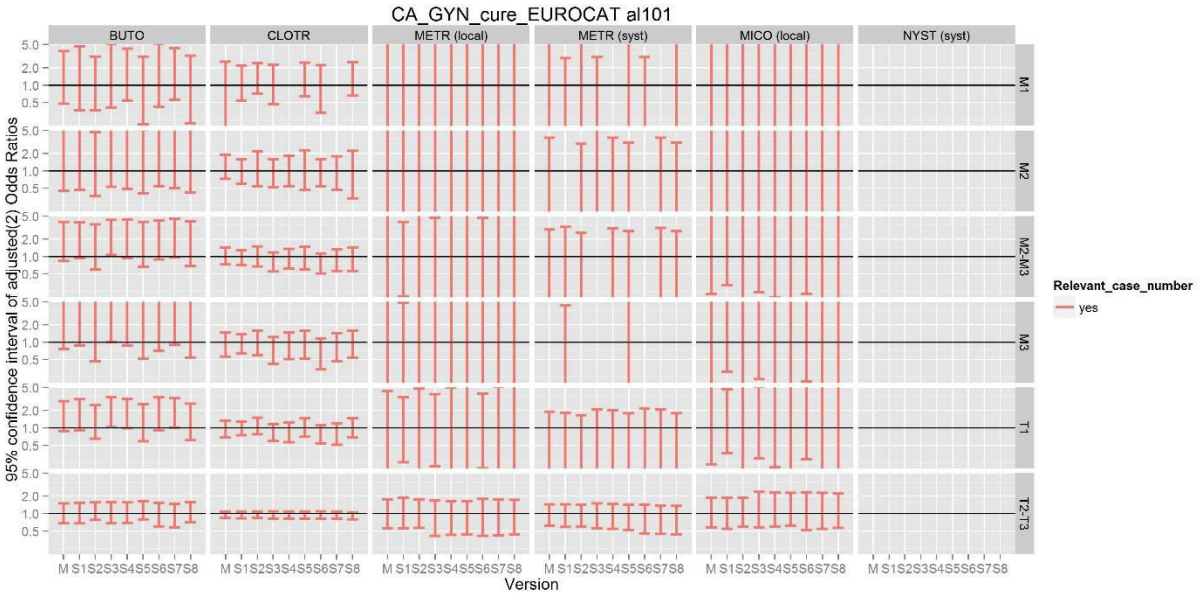
	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	809	1.64 *
Excluding single outpatient reports (S3-S5)	718	1.45 *
Excluding all outpatient reports (S6-S8)	695	1.41 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		1.00 **

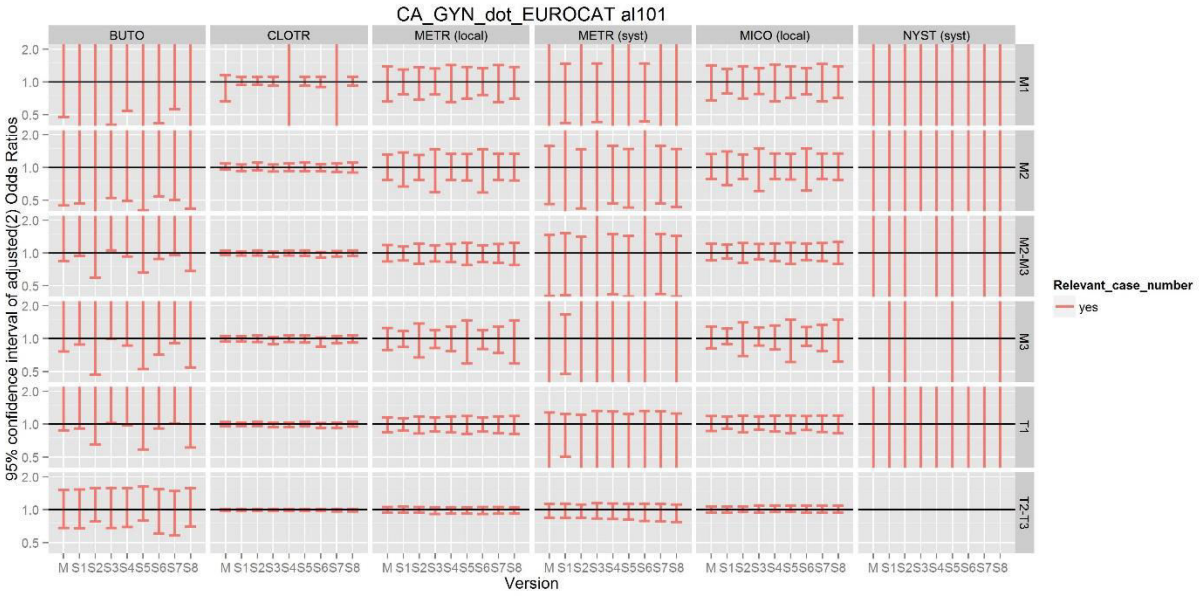
*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

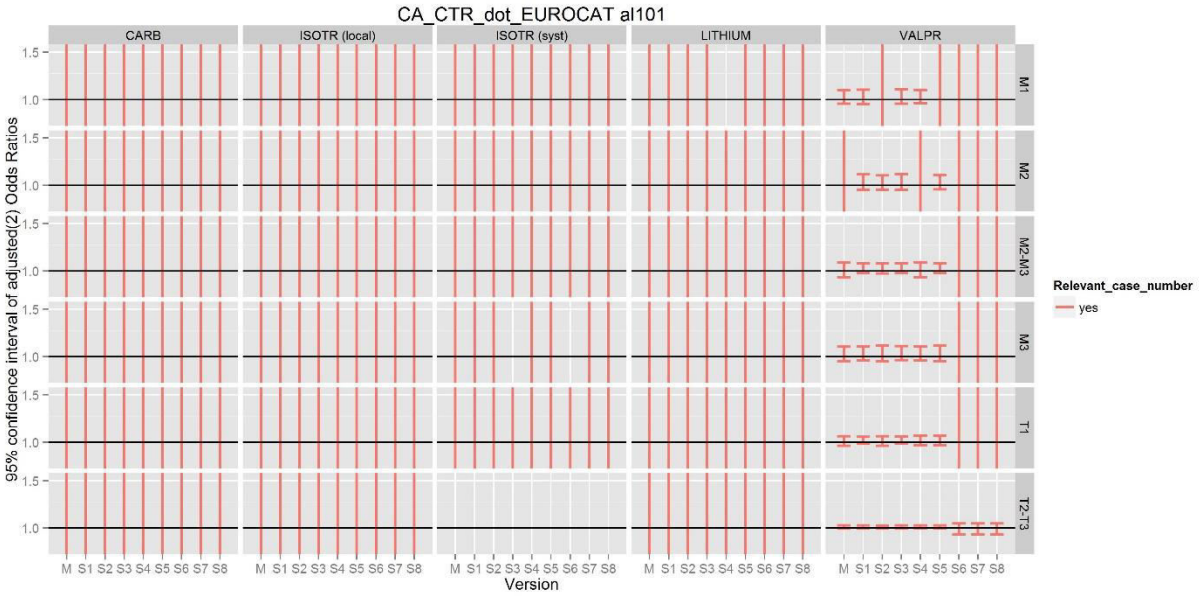
Based on the above numbers, the exclusion of single or all outpatient reports did not meaningfully reduce the number of al101 cases in the study. The observed rate is consistent with the national statistics (assuming some underreporting of inpatient and outptient cases to the registry). Acordingly, the main and sensitivity analyses have similar relevance for the analysis of this code group.Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.J. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.J. 95% confidence intervals of odds ratios of drug exposure in the al101 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).




CA_GYN_dot_EUROCAT al101
BUTO
CLOTR
METR (local)
METR (syst)
MICO (local)
NYST (syst)
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
M S1S2S3S4S5S6S7S8
Version
Relevant_case_number
yes


CA_CTR_dot_EUROCAT al101
CARB
ISOTR (local)
ISOTR (syst)
LITHIUM
VALPR
M1
M2
M2-M3
M3
T1
T2-T3
95% confidence interval of adjusted(2) Odds Ratios
M S1 S2 S3 S4 S5 S6 S7 S8
Version
Relevant_case_number
yes

15.3.12. Digestive system (EUROCAT al40)

The EUROCAT al40 code group has been defined as any reported ICD code in the Q38-Q45 and Q790 ranges.

	No. of cases	Rate per 1,000 live births
All outpatient reports included (Main analysis, S1-S2)	6650	13.47 *
Excluding single outpatient reports (S3-S5)	2900	5.88 *
Excluding all outpatient reports (S6-S8)	2760	5.59 *
2011 Annual Report of the Hungarian Congenital Abnormality Registry		3.73 **

*Number of cases divided by 493,535 live births in the study; **Sum of reported rates with individual codes – may overestimate the overall rate as multiple relevant codes could be reported from the same case {OEFI, 2013 #60}.

Based on the above numbers, single outpatient reports may be unreliable for the analysis of these anomalies; hence, sensitivity analyses S3-S8 are the most relevant ones for the analysis of this code group.

Confidence intervals of the fully adjusted odds ratios are shown in Figure 15.K. For a full tabular summary of all Amendment 2 congenital anomaly study results, please see Section 15.1.

Figure 15.K. 95% confidence intervals of odds ratios of drug exposure in the al40 congenital anomaly group, adjusted to all confounders.

Gynecology drug exposure is expressed in cure number (first panel) or in days of therapy (second panel). Exposure to active control drugs is expressed in days of therapy (third panel). BUTO, butoconazole; CLOTR, clotrimazole; METR, metronidazole; MICO, miconazole; NYST, nystatine; CARB, carbamazepine; ISOTR, isotretinoin; VALPR, valproic acid; syst, systemic; M1, M2 and M3, first, second and third month of pregnancy; T1, T2, T3, first, second and third trimester. M, main analysis; S1-S8, sensitivity analyses. Missing error bars indicate the lack of model results (insufficient exposure).