Received: 19 August 2024 | Revised: 21 November 2024 | Accepted: 13 December 2024

DOI: 10.1111/aogs.15052

AOGS Acta Obstetricia et Gynecologica Scandinavica

ORIGINAL RESEARCH

Exposure to potentially teratogenic medications before and during the first trimester of pregnancy compared to women of childbearing age: A retrospective analysis of Swiss claims data (2015–2021)

Carole A. Marxer[1,2] | Sereina M. Graber[3] | Daniel Surbek[4] | Alice Panchaud[5,6,7] | Christoph R. Meier[1,2] | Julia Spoendlin[1,2]

[1]Hospital Pharmacy, University Hospital Basel, Basel, Switzerland

[2]Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland

[3]Department of Health Sciences, Helsana Insurance Group, Zurich, Switzerland

[4]Department of Obstetrics and Gynaecology, University Hospital Bern, University of Bern, Bern, Switzerland

[5]Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland

[6]Service of Pharmacy, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

[7]Materno-Fetal and Obstetrics Research Unit, Department "Femme-Mère-Enfant", Lausanne University Hospital, Lausanne, Switzerland

Correspondence
Julia Spoendlin, Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacy and Epidemiology, University of Basel and Hospital Pharmacy, University Hospital Basel, Schanzenstrasse 9, 4031 Basel, Switzerland.
Email: julia.spoendlin@unibas.ch

Abstract

Introduction: Exposure to potentially teratogenic medications during pregnancy is underinvestigated in Switzerland. We aimed to assess exposure to potential teratogens preconceptionally, during the first trimester, and in women of childbearing age, and specifically explore the effectiveness of the valproate pregnancy prevention program (2018).

Material and Methods: Retrospective study using the Swiss Helsana claims database. In a pregnancy cohort (2015–2021) and a cohort of women of childbearing age (2021 and 2018), we defined three 90-day time periods: (1) first trimester, (2) preconceptional period (days 180–90 before pregnancy), and (3) January 01, 2021, and March 31, 2021 (women of childbearing age). During all periods, we quantified the exposure prevalence to at least one dispensed weak, proven, and unequivocally potent teratogen overall and by age strata. We quantified the exposure prevalence to each individual teratogen, and to valproate during pregnancy by calendar year to compare its use before and after the introduction of a pregnancy prevention program (2018). We investigated the use of systemic retinoids particularly isotretinoin in women of childbearing age.

Results: Of 34 584 pregnant women, 1.4% were exposed to potential teratogens during the first trimester (weak: 1.3%, proven: 0.06%, unequivocally potent: 0.04%). During the preconceptional period, 2.9% were exposed to any teratogen compared to 4.7% of women of childbearing age (N_{total} = 95 059). Systemic glucocorticoids were the most prevalent weak teratogens during all time periods (75% of all claimed teratogens during the first trimester). In the first trimester, the antibiotic cotrimoxazole and the thyreostatic thiamazole (weak teratogens), ranked second and third, followed

Abbreviations: ASM, antiseizure medication; ATC, Anatomical Therapeutic Chemical classification system; IQR, interquartile range; LMP, last menstrual period; MCM, major congenital malformations; SwissDRG, Swiss Diagnosis Related Groups.

by the antiseizure medications carbamazepine and topiramate (proven teratogens). Among women of childbearing age, exposure to weak and proven teratogens increased with age, whereas exposure to unequivocally potent teratogens decreased with age. This was due to 2.3% of women <26 years who claimed systemic isotretinoin. Valproate use during pregnancy decreased after the introduction of a pregnancy prevention program (2.39/10 000 pregnancies [2015–2018] vs. 0.93/10 000 pregnancies [2019–2021]).

Conclusions: Most medications with potential teratogenic effects dispensed to women of childbearing age and pregnant women were in the group of weak teratogenicity level, and many women discontinued treatment before pregnancy. Preliminary evidence suggests the valproate pregnancy prevention program in Switzerland may be beneficial.

KEYWORDS
congenital malformations, observational research, pharmacoepidemiology, pregnancy, Swiss healthcare data, systemic retinoids, teratogens, valproate

1 | INTRODUCTION

Drug treatment during pregnancy requires careful consideration of potential risks and benefits. Insufficiently treated maternal diseases may put pregnant women and the unborn child at risk, but *in utero* exposure to potential teratogens during critical risk windows of pregnancy may cause congenital malformations, especially during the first trimester. According to a German survey study,[1] women became aware of their pregnancy on average in week 3 after conception (week 5 after the last menstrual period, LMP), and the first consultation with a medical professional was not until week 5 after conception. Organogenesis of the embryo begins in week 3 after conception, which is when sensitive organs such as the neural tube start to form.[2] Given that up to 50% of pregnancies are unplanned,[3] use of potential teratogens is critical for all women of childbearing age.

Exposure to potential teratogens during pregnancy and in women of childbearing age in Switzerland is not well understood. Few Swiss studies specifically evaluated the use of selected teratogens for specific indications during pregnancy[4–6] and in women of childbearing age,[6] but the overall use of potential teratogens by this population of interest remains unknown. A German claims data study reported that 663 of 66 549 (1.00%) pregnant women were dispensed a potentially teratogenic drug during the first trimester in 2018. Of all teratogens, 92% ($n = 611$) were weak teratogens (excess risk of major congenital malformations (MCM) between 0.1% and 1.0%[1]), 5% ($n = 32$) were proven teratogens (excess MCM risk: 3%–10%), and 3% ($n = 20$) were unequivocally potent teratogens (excess MCM risk: 10%–30%).[7]

We aimed to conduct a retrospective descriptive study using Swiss claims data of the health insurance Helsana group to evaluate exposure to potential teratogens during the first trimester of pregnancy (2015–2021) compared to a preconceptional period in the same women as well as to a cohort of women of childbearing age (2021 and 2018) in outpatient care in Switzerland. We further aimed to explore the potential effect of the valproate pregnancy prevention program introduced in 2018.

Key Message

In Switzerland, potentially teratogenic medications were often discontinued before conception. Most teratogens dispensed during the first trimester were weak teratogens. The number of pregnancies exposed to valproate declined after the introduction of the pregnancy prevention program, but sample size was small.

2 | MATERIAL AND METHODS

2.1 | Study design, data source

We conducted a retrospective study using the anonymized Helsana claims database (2015–2021). The Helsana group is one of Switzerland's largest health insurance companies, covering around 1.2 million individuals with mandatory health insurance from all 26 cantons (around 15% of residents in Switzerland). The database captures demographics, outpatient healthcare services (TARMED codes), outpatient drug dispensations (Anatomical Therapeutic Chemical classification system, ATC codes), as well as bundled diagnostic codes for hospitalizations (Swiss Diagnosis Related Groups, SwissDRG).

2.2 | Study populations

We established two separate study populations, a pregnancy cohort, and a cohort of women of childbearing age.

2.3 | Pregnancy cohort

The pregnancy cohort included pregnancies of women between 13 and 49 years of age at delivery who delivered between January 1, 2015, and December 31, 2021, and were covered by mandatory health insurance. All women were (1) continuously insured with Helsana's mandatory health insurance between 270 days before the start of pregnancy until 270 days after the delivery date and (2) not pregnant during the preconception or postpartum period (determined by recorded codes for delivery or abortion reported in the Table S1). A woman may have contributed more than one pregnancy to the study population. Of note, this study population was used in another study evaluating drug use after delivery.[8] This is the reason why we required continuous enrolment after delivery, although the postpartum period is not subject of this study.

2.3.1 | Identification of pregnancies and definition of the delivery date

We identified inpatient and outpatient deliveries (live births and stillbirths). Inpatient deliveries were captured by means of recorded SwissDRG codes, and outpatient deliveries by means of recorded TARMED codes (billing system for outpatient services) or billed deliveries by midwifes (Table S1). In case of multiple delivery codes recorded within a period of 30 days, these were regarded as pertaining to the same pregnancy,[9] and the first recorded code was set as the date of delivery. Delivery codes separated by more than 300 days were considered as two separate pregnancies. When two subsequent codes were separated between 30 and 300 days, the delivery date was set at the inpatient SwissDRG code and pregnancies were excluded if only outpatient codes were recorded.[4–6] Deliveries of twins were treated as one single pregnancy. A flow chart showing the number of excluded pregnancies is displayed in Figure 1.

2.3.2 | Identification of the date of the LMP and pregnancy trimesters

The date of the LMP (i.e., start of pregnancy) was estimated because gestational length or start of pregnancy was not recorded in Swiss claims data during the study period. According to an algorithm validated in US claims data,[10] the date of the LMP was assigned to be 245 days before the date of delivery for pregnancies that had a SwissDRG code indicative of preterm delivery (<37 weeks, O01A, O01B, O01C, O01D, and O60A), and 270 days before the date of delivery for all other pregnancies. This algorithm was used in previous studies evaluating pregnancies based on the Helsana claims database.[4–6]

2.3.3 | Observation period

The observation period was defined as the time between 270 days before LMP and the delivery date. All eligible pregnancies had to be enrolled with the Helsana group during the entire observation period. We divided the observation period into a 270-day preconceptional period (before LMP) and a pregnancy period between LMP and delivery. The pregnancy period was further divided into trimesters, which were each 90 days, whereby the third trimester was shortened in case of a SwissDRG code indicative of preterm delivery.

2.4 | Cohort of women of childbearing age

The cohort of women of childbearing age included all women aged 13–49 years in 2021 (2018 in additional analyses), irrespective of whether they were pregnant or not. Women had to be continuously insured with Helsana's mandatory health insurance for the entire year (1 January until 31 December in respective year) and were frequency matched to pregnant women in the pregnancy population based on age (calendar year) to assure the same age distribution among both cohorts.

2.5 | Time windows of interest

We compared exposure to potential teratogens during the 90-day first trimester to two 90-day time periods during (1) the preconceptional period between (including) days 180–90 before LMP and (2) a 90-day period in women of childbearing age in 2021 and 2018 (January 1. until April 1; Figure 2).

2.6 | Covariates and descriptive analyses

For all pregnancies, we captured maternal age at delivery and the year of delivery. For women of childbearing age, we captured age on January 1 of the respective year. For comparability, we captured the same teratogens as a prior study based on German claims data of the health insurance BARMER (2021).[1] Teratogens were categorized into weak, proven, and unequivocally potent teratogens according to Dathe and Schäfer (Table 1).[7] Weak teratogens cause an approximate excess of 0.1%–1.0% of MCM in children after the first trimester *in utero* exposure, whereas this number is 1%–10% for proven teratogens, and over 10% for unequivocally potent teratogens. According to the German study, we additionally included all teratogens, which are subject to a pregnancy-related risk management plan in Germany due to teratogenicity. These additional teratogens were all classified as unequivocally potent teratogens. Drug claims were identified based on recorded ATC codes (Table 1).

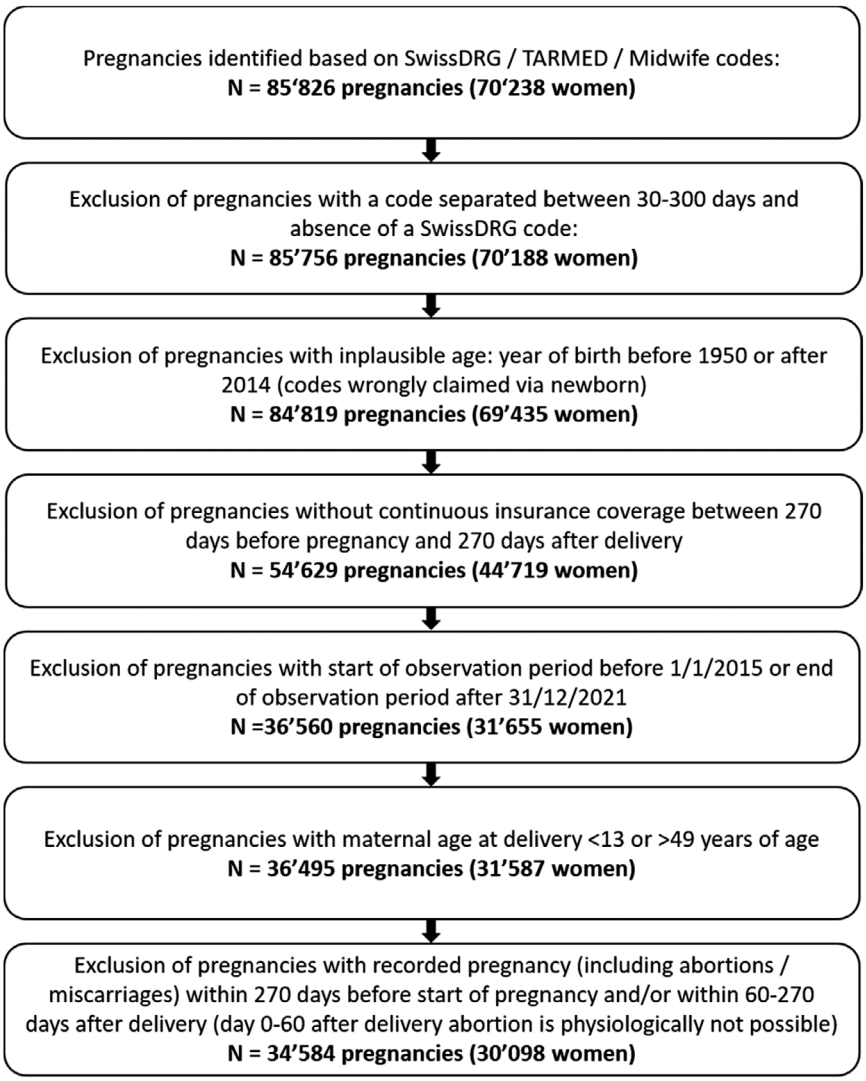

FIGURE 1 Flow chart of the pregnancy cohort.

2.6.1 | Prevalence of exposure to dispensed potential teratogens

We quantified the prevalence of exposure to dispensed potential teratogens by category of teratogenicity in the pregnancy cohort (90-day preconceptional period and first trimester) and in the cohort of women of childbearing age (90-day period in 2021 and 2018 separately) overall and within age strata. We decided to evaluate these two time periods to ensure that the COVID-19 pandemic and the related restrictions in health care did not impact our results. Prevalence of exposure is presented as proportion of women exposed to ≥1 potential teratogen of interest divided by the total number of pregnancies.

We further quantified the prevalence of exposure to each individual teratogen separately during the three time periods of interest and present results in descending order as absolute numbers per 10 000 women/pregnancies.

To evaluate the robustness of our analyses, we also compared the full 270-day preconceptional period to a 270-day period in the cohort of women of childbearing age (January 1, 2021, to September 28, 2021; Figure 2: Depiction of time windows) in a sensitivity analysis.

2.6.2 | Prevalence of exposure to systemic retinoids (post-hoc analysis)

Systemic retinoids were the most prevalent unequivocally potent teratogens in women of childbearing age. Therefore, we performed an additional analysis to quantify (1) the prevalence of exposure to systemic retinoids in women of childbearing age by age group and (2) the prevalence of systemic isotretinoin, which accounted for almost all claimed systemic retinoids.

2.6.3 | Prevalence of exposure to valproate by year

A special focus of this study was on the antiseizure medication (ASM) valproate, for which a pregnancy prevention program has been introduced in Switzerland in December 2018.[11] We quantified the prevalence of exposure to valproate in the pregnancy cohort during the entire pregnancy (overall and by trimester) by calendar year between 2015 and 2021, presented as absolute numbers of exposed pregnancies per 10 000 pregnancies. We compared the mean (SD) prevalence

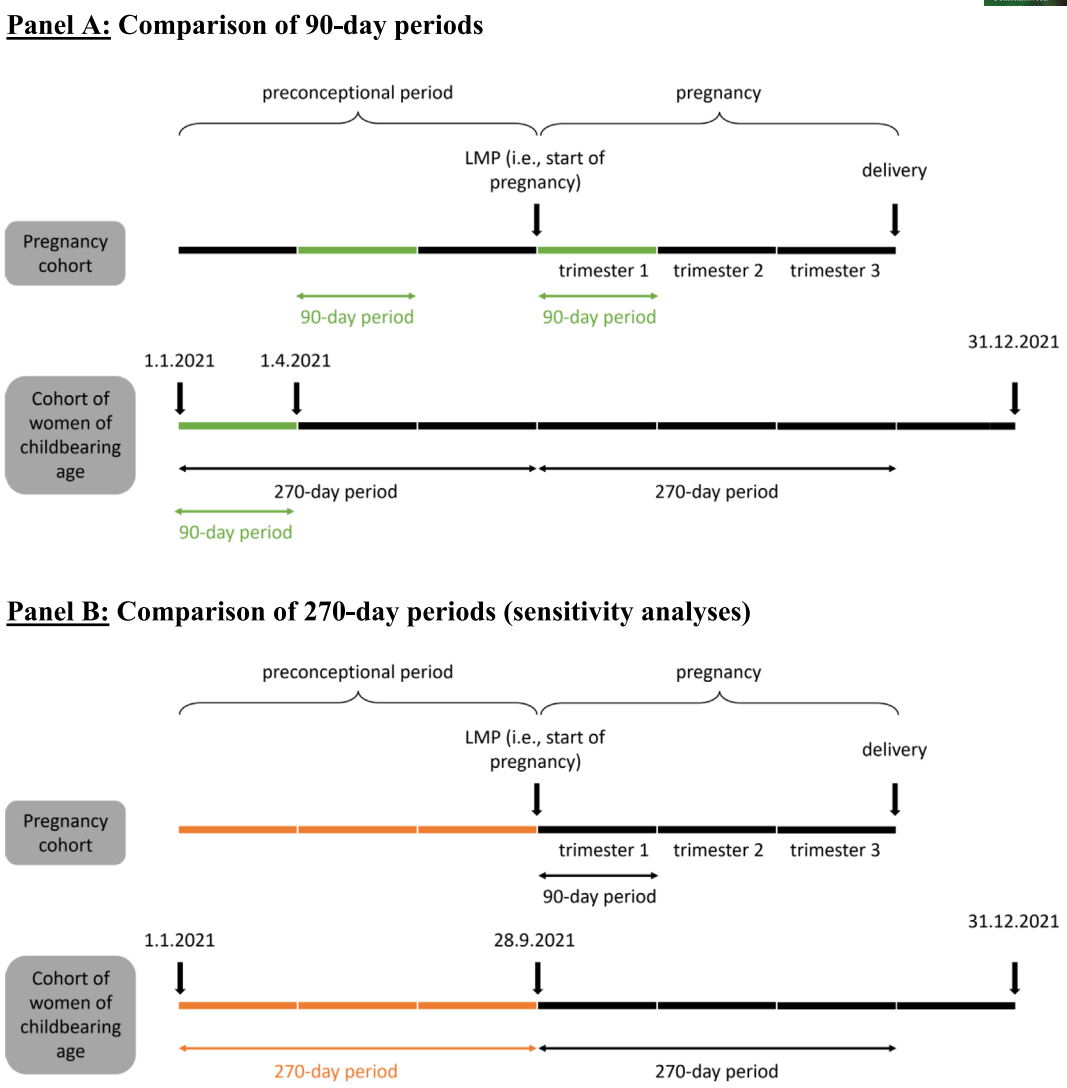

FIGURE 2 Time windows used in analyses.

before and after the introduction of the pregnancy prevention program in Switzerland (2015–2018 vs. 2019–2021). To account for the fact that LMP was estimated and might deviate from the true LMP in some cases, we conducted a sensitivity analysis in which we quantified the prevalence of exposure to valproate during pregnancy after excluding exposures within 14 days after LMP.

Analyses were conducted using *Python 3.0*.[12]

3 | RESULTS

3.1 | Demographics and characteristics

We included 34 584 pregnancies of 30 098 women in the pregnancy cohort (Figure 1), and 95 059 women in the cohort of women of childbearing age. The median age of women was 32 years (interquartile range [IQR] = 29–36) in both cohorts. In total, 10.2% were aged <26 years, 62.4% between 26 and 35 years, and 27.4% ≥36 years. The median maternal age at delivery was consistent with the overall maternal age in Switzerland during this time.[13]

3.2 | Prevalence of exposure to at least one teratogen

During the first trimester, 1.4% ($n = 476$) of pregnant women were exposed to at least one potential teratogen, compared to 2.9% ($n = 1003$) during the 90-day preconceptional period and 4.7% ($n = 4\,416$) of women of childbearing age. In total, 1.3% ($n = 445$) of pregnant women were exposed to at least one weak teratogens during the first trimester, 0.06% ($n = 22$) to a proven teratogen, and 0.04% ($n = 13$) to unequivocally potent teratogens (Table 2 and Figure 3). Among the 4.7% women of childbearing age who were exposed to at least one teratogen, 3.3% ($n = 3102$) were exposed to weak teratogens, 0.5% ($n = 474$) to proven teratogens, and 1.1% ($n = 1\,011$) to unequivocally potent teratogens. Increasing age

TABLE 1 Teratogens by level of teratogenicity based on the German BARMER drug report (2021)[1] adapted from Dathe and Schaefer (2019).[7]

Drug substance	ATC code/s	Signs and symptoms in the newborn/ primarily affected organ systems
Unequivocally potent teratogens (monotherapy is associated with an up to 10-fold (30%) increased risk of gross structural malformations)		
Weak teratogens (risk 1:100 to 1:1000 exposed fetuses)		
Systemic glucocorticoids	H02AB, H02BX (without H02BX21)	Palate
Lithium	N05AN01	Heart (Ebstein anomaly, very rare)
Thiamazole/carbimazole	H03BB01, H03BB02, H03BB52	Choanal atresia, tracheo-esophageal fistulas, aplasia cutis
Trimethoprim/sulfamethoxazole	J01EA01, J01EE01, J01EE02, J01EE03, J01EE04, J01EE05, J01EE07, J01EE51, J04AM08, R05GC02	Neural tube defect
Proven teratogens (monotherapy is associated with an up to threefold (10%) increased risk of gross structural malformations)		
Androgens	G03B, G03E	Masculinization
Carbamazepine	N03AF01	Neural tube defect, heart, palate, urogenital system, extremities, dysmorphic facial features
Coumarin derivatives (warfarin, phenprocoumon)	B01AA03, B01AA04	Nose, extremities
Cyclophosphamide	L01AA01	Multiple malformations
Methotrexate[a]	L04AX03, M01CX01	Multiple malformations
Misoprostol (for attempted induction of abortion)	Not included in our analyses[b]	Moebius sequence, extremities
Penicillamine	M01CC01	Cutis laxa
Phenobarbital/primidone	N03AA02, N03AA03	Heart, palate, urogenital system, extremities, dysmorphic facial features
Phenytoin	N03AB02, N03AB52	Heart, palate, urogenital system, extremities, dysmorphic facial features
Topiramate	N02CX12, N03AX11	Palate
Vitamin A (significantly more than 25′000IU retinol/day)	Not included in our analyses[c]	Ear, central nervous system, heart, skeleton
Cytostatics	L01A (L01AA01 counted as separate teratogen: cyclophosphamide), L01BA (L01BA01 counted as separate teratogen: methotrexate), L01CA, L01CB, L01CC, L01CD, L01D, L01XA, L01XB, L01XE, L01XY, L02 (without L02AA, L02AB, L02AE, L02AX, L02BG, L02BX, because also used in reproductive medicine[d]), V70BA	Multiple malformations
Unequivocally potent teratogens (monotherapy is associated with an up to 10-fold (30%) increased risk of gross structural malformations)		
Systemic retinoids (etretinate, acitretin, isotretinoin, alitretinoin, tretinoin)	D05BB01, D05BB02, D10BA01, D11AH04, L01XX14	Ear, central nervous system, heart, skeleton
Thalidomide (−derivatives)	L04AX02, L04AX04, L04AX06	Extremities, multiple malformations
Mycophenolate	L04AA06	Ear, palate
Valproate	N03AG01	Neural tube defect (lumbar spina bifida), heart, palate, urogenital system, extremities, dysmorphic facial features
Further unequivocally potent teratogens	Bosentan (C02KX01), ambrisentan (C02KX02), macitentan (C02KX04), tolvaptan (C03XA01, G04BX21), cladribine (L01BB04, L04AA40), vismodegib (L01XX43), sonidegib (L01XX48), leflunomide (L04AA13), fingolimod (L04AA27), teriflunomide (L04AA31), ozanimod (L04AA38), siponimod (L04AA42), hydroxycarbamide (L01XX05), und baricitinib (L04AA37)	Multiple malformations

[a]Risk associated with antirheumatic doses is lower.

[b]We did not include misoprostol due to its off-label use for medical abortions and for labor induction.

[c]We did not consider vitamin A, because teratogenicity only occurs at doses above 25000IU retinol/day, and daily doses are unknown in claims data.

[d]Not excluded in the 2021 BARMER drug report,[1] but excluded in our study, because of a potentially less accurate estimation of the LMP in our study which may cause exposure misclassification of those specific treatments.

TABLE 2 Prevalence of exposure to at least one dispensed teratogen by teratogenicity level in the cohort of women of childbearing (2021) and the pregnancy cohort (2015–2021, preconceptional period and first trimester) overall and by maternal and women's age strata.

	Cohort of women of childbearing age (90 days)				Pregnancy cohort: Preconceptional period (90 days)				Pregnancy cohort: First trimester (90 days)			
	Overall	<26 years	26–35 years	≥36 years	Overall	<26 years	26–35 years	≥36 years	Overall	<26 years	26–35 years	≥36 years
N	95 059	9 655	59 348	26 056	34 584	3 513	21 592	9 479	34 584	3 513	21 592	9 479
Any teratogen	4 416 (4.69)	5 53 (5.73)	2 498 (4.20)	1 365 (5.24)	1 003 (2.90)	111 (3.16)	625 (2.89)	267 (2.82)	476 (1.38)	36 (1.02)	267 (1.24)	173 (1.83)
Weak teratogen	3 102 (3.26)	275 (2.85)	1787 (3.01)	1 040 (3.99)	899 (2.60)	91 (2.59)	566 (2.62)	242 (2.56)	445 (1.29)	34 (0.97)	247 (1.14)	164 (1.73)
Proven teratogen	474 (0.50)	50 (0.52)	241 (0.41)	183 (0.70)	57 (0.16)	<10 (<0.50)	32 (0.15)	18 (0.19)	22 (0.06)	<10 (<0.10)	15 (0.07)	<10 (<0.10)
Unequivocally potent teratogens	1 0 11 (1.06)	249 (2.58)	511 (0.93)	211 (0.81)	56 (0.16)	13 (0.37)	33 (0.15)	10 (0.11)	13 (0.04)	<10 (<0.10)	<10 (<0.10)	<10 (<0.10)

Note: Values are the number (%) unless indicated otherwise.
Abbreviation: *N*, number.

correlated with the proportion of women exposed to weak (<26: 2.9%, ≥36: 4.0%) and proven teratogens (<26: 0.5%, ≥36: 0.7%). The sensitivity analysis (comparing 270-day periods) showed the same patterns, but prevalence of exposure was higher (i.e., longer time window, Table S2).

3.3 | Prevalence of exposure to individual potential teratogens

Overall, all teratogens were less frequently dispensed during the 90-day preconceptional period compared to women of childbearing age, and again less frequently during the first trimester. The top five most frequently dispensed potential teratogens were similar in women of childbearing, during preconceptional, and during the first trimester, although with some important differences.

Systemic glucocorticoids were the most prevalent weak teratogens during all time periods with 103.8/10 000 women exposed during the first trimester (i.e., 1.0%), 207.6/10 000 during the preconceptional period (i.e., 2.1%), and 262.8/10 000 of women of childbearing age (i.e., 2.6%).

In the first trimester, the systemic antibiotic trimethoprim with combined sulfamethoxazole (cotrimoxazole) was the second most prevalent teratogen (21.7/10 000, weak teratogen) followed by the thyreostatic thiamazole/carbimazole (3.2/10 000, weak teratogen), and the ASM carbamazepine (2.6/10 000) and topiramate (2.6/10 000), which are both proven teratogens (Table 4). During the preconceptional period and among women of childbearing age, these potential teratogens were also among the most frequently observed (except carbamazepine) with higher prevalence of exposure (Table 4). Systemic retinoids were substantially more prevalent among women of childbearing age being the second most prevalent teratogens (unequivocally potent, 79.2/10 000) and the third most prevalent during the preconceptional period (9.8/10 000, Tables 3 and 4). During the first trimester, systemic retinoids were claimed during 1.2/10 000 pregnancies (7th most frequently claimed teratogen). In the *post-hoc* analysis evaluating exposure to systemic retinoids among women of childbearing age, we found that exposure to unequivocally potent teratogens was highest among women aged <26 years (2.5% vs. 0.8% in women ≥36 years, Table 2). This inverse correlation was due to relatively high exposure of younger women of childbearing age to systemic retinoids (98% of women <26 years with at least one unequivocally potent teratogen, of which all were systemic isotretinoin; Table 3).

The ASM valproate (unequivocally potent teratogen) was the 8th most frequently dispensed teratogen and the second most frequently dispensed ASM with teratogenic potential among women of childbearing age (10.8/10 000 women), preceded by the less teratogenic but proven teratogen topiramate (20.1/10 000 women), and followed by carbamazepine (3.6/10 000). In the preconceptional period, valproate was claimed by 3.2/10 000 women (second most frequent ASM), whereas during the first trimester, valproate was the third most frequently dispensed ASM with teratogenic potential (1.4/10 000 pregnancies), preceded by topiramate and carbamazepine (Table 4).

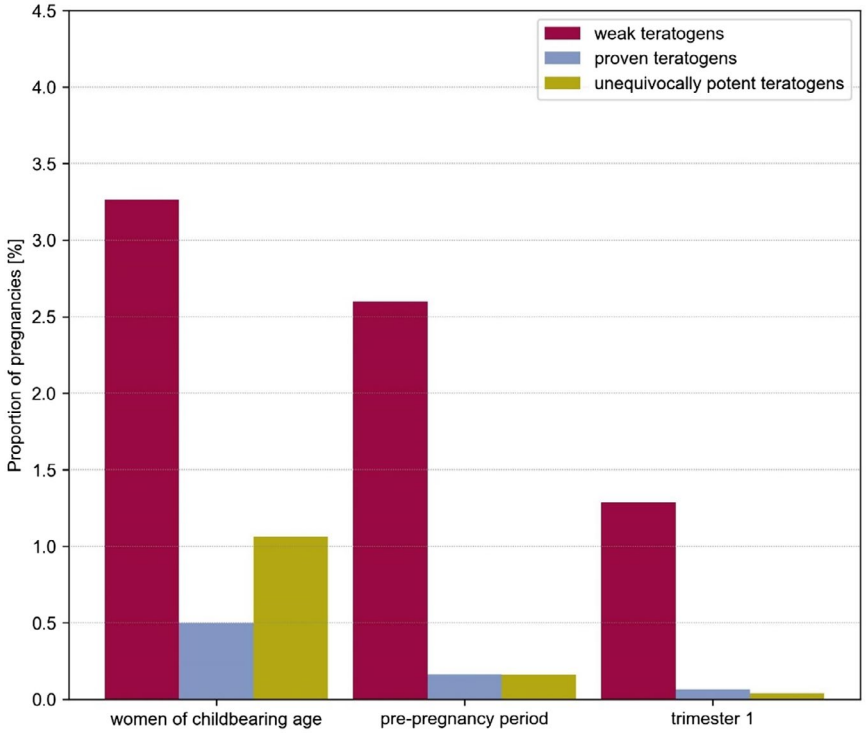

FIGURE 3 Prevalence of exposure to at least one dispensed teratogen by teratogenicity level in the cohort of women of childbearing age (90-day period in 2021) and in the pregnancy cohort (90-day preconceptional period and 90-day first trimester between 2015 and 2021).

	Overall	<26 years	26–35 years	≥36 years
Number of women of childbearing age	95 059	9 655	59 348	26 056
Unequivocally potent teratogens	1.09%	2.53%	0.94%	0.82%
Systemic retinoids	0.81%[a]	2.34%[b]	0.70%	0.42%
Systemic isotretinoin	0.80%[c]	2.34%[d]	0.69%	0.40%

[a]74.31% of women of childbearing age who were exposed to unequivocally potent teratogens.
[b]92.49% of women of childbearing age <26 years of age who were exposed to unequivocally potent teratogens.
[c]98.77% of women of childbearing age who were exposed to systemic retinoids.
[d]100% of women of childbearing age <26 years of age who were exposed to systemic retinoid.

TABLE 3 Prevalence of exposure to at least one dispensed unequivocally potent teratogen and separate for systemic retinoids (most frequent unequivocally potent teratogen), and systemic isotretinoin (most frequent systemic retinoid) in women of childbearing age (2021) by age strata.

The sensitivity analysis (comparing 270-day periods) showed the same patterns, but absolute numbers per 10 000 women/pregnancies were higher (i.e., longer time window; Table S3).

3.4 | Additional analyses (women of childbearing age in 2018 vs. 2021)

When comparing our results among women of childbearing age identified in 2018 instead of 2021, we found similar patterns in the use of teratogens (Tables S5–S7, Figure S1).

3.5 | Prevalence of exposure to valproate by year

The mean prevalence of exposure to valproate during pregnancy was lower after the introduction of the pregnancy prevention program in Switzerland in December 2018 (2.39/10 000 pregnancies in 2015–2018 vs. 0.93/10 000 pregnancies in 2019–2021, Table 5, Table S4). These results did not change when ignoring exposures to valproate during the first 14 days after LMP.

4 | DISCUSSION

This study used Swiss claims data to evaluate exposure to outpatient-dispensed potential teratogens in the first trimester of pregnancy (2015–2021), compared to comparable time periods before pregnancy and among women of childbearing age.

Exposure to teratogens was highest in women of childbearing age (4.7%) and lower before pregnancy (2.9%) and during the first trimester (1.4%). This suggests that potential teratogenic risks are considered when planning to become pregnant and treatment changes are undertaken, but it may also indicate general caution in

TABLE 4 Prevalence of exposure to each individual teratogen in descending order in the cohort of women of childbearing age (90-day period in 2021) and in the pregnancy cohort (2015–2021; 90-day preconceptional period vs. 90-day first trimester).

Cohort of women of childbearing age (90 days)		Pregnancy cohort: Preconceptional period (90 days)		Pregnancy cohort: First trimester (90 days)	
Teratogen [teratogenicity category[a]]	**/10 000 women**	**Teratogen [teratogenicity category[a]]**	**/10 000 pregnancies**	**Teratogen [teratogenicity category[a]]**	**/10 000 pregnancies**
Glucocorticoids (systemic) [1]	262.8	Glucocorticoids (systemic) [1]	207.6	Glucocorticoids (systemic) [1]	103.8
Retinoids (systemic) [3]	79.2	Trimethoprim/ sulfamethoxazole [1]	46.8	Trimethoprim/ sulfamethoxazole [1]	21.7
Trimethoprim/ sulfamethoxazole [1]	48.0	Retinoids (systemic) [3]	9.8	Thiamazole/carbimazole [1]	3.2
Topiramate [2]	20.1	Thiamazole/carbimazole [1]	7.2	Carbamazepine [2]	2.6
Thiamazole/carbimazole [1]	13.6	Topiramate [2]	5.5	Topiramate [2]	2.6
Methotrexate [2]	13.0	Methotrexate [2]	4.3	Valproate [3]	1.4
Further unequivocally potent teratogens [3][b]	10.8	Valproate [3]	3.2	Retinoids (systemic) [3]	1.2
Valproate [3]	10.8	Cytostatics [2]	2.3	Further unequivocally potent teratogens [3][b]	1.2
Cytostatics [2]	8.9	Carbamazepine [2]	3.2	Coumarin derivate (phenprocoumon) [2]	0.6
Lithium [1]	7.3	Further unequivocally potent teratogens [3][b]	2.3	Lithium [1]	0.6
Carbamazepine [2]	3.6	Coumarin derivate (phenprocoumon) [2]	1.2	Methotrexate [2]	0.6
Mycophenolate [3]	3.1	Mycophenolate [3]	0.9	Androgens [2]	0.3
Coumarin derivate (phenprocoumon) [2]	2.1	Lithium [1]	0.8	Cyclophosphamide [2]	0.0
Cyclophosphamide [2]	1.4	Cyclophosphamide [2]	0.0	Penicillamine [2]	0.0
Phenobarbital/primidone [2]	1.6	Androgens [2]	0.0	Phenobarbital/primidone [2]	0.0
Androgens [2]	0.9	Coumarin derivative (warfarin) [2]	0.0	Phenytoin [2]	0.0
Phenytoin [2]	0.2	Penicillamine [2]	0.0	Coumarin derivative (warfarin) [2]	0.0
Thalidomide (−derivatives) [3]	0.0	Phenobarbital/primidone [2]	0.0	Mycophenolate [3]	0.0
Coumarin derivative (warfarin) [2]	0.0	Phenytoin [2]	0.0	Thalidomide (−derivatives) [3]	0.0
Penicillamine [2]	0.0	Low-dose methotrexat [1]	0.0	Low-dose methotrexat [1]	0.0
Low-dose methotrexat [1]	0.0	Thalidomide (−derivatives) [3]	0.0	Cytostatics [2]	0.0

[a][1] = weak teratogen, [2] = proven teratogen, [3] = unequivocally potent teratogens.

[b]Bosentan, ambrisentan, macitentan, tolvaptan, cladribine, vismodegib, sonidegib, leflunomide, fingolimod, teriflunomide, ozanimod, siponimod, hydroxycarbamide, und baricitinib.

prescribing medications to pregnant women. However, the higher exposure to teratogens among women of childbearing age needs to be interpreted cautiously, given the fact that we did not have information on contraception, which is not reimbursed in Switzerland. Women of childbearing age, who are exposed to potential teratogens, may have taken precautions not to get pregnant.

It is reassuring that most women who were exposed to teratogens during the first trimester (1.3%, $n = 445$) claimed weak teratogens (93.5% of all claimed teratogens) and the majority claimed systemic glucocorticoids (1.0%). This was comparable to results from a German claims-based study, where 1.0% of pregnant women were exposed to teratogens during the first trimester, of which 91.2% were weak.[1] Weak teratogens cause an approximate excess of 0.1%–1.0% of MCM in children after first trimester *in utero* exposure, whereas this number is 1%–10% for proven teratogens, and over 10% for unequivocally potent teratogens. In the absence of safer or effective alternatives, weak teratogens and sometimes also proven teratogens may be clinically indicated and may be the treatment of choice after careful consideration of potential harms and benefits.

	Pregnancy	First trimester	Second trimester	Third trimester
By year [/10 000 pregnancies]				
2015	2.00	1.00	1.00	2.00
2016	3.08	1.03	2.05	1.03
2017	2.20	1.10	0.00	1.10
2018	2.29	2.29	1.15	1.15
2019	1.07	1.07	0.00	0.00
2020	0.94	0.00	0.94	0.00
2021	0.78	0.00	0.00	0.78
Mean (SD)				
2015–2018	2.39 (0.41)	1.35 (0.54)	1.05 (0.73)	1.32 (0.40)
2019–2021	0.93 (0.12)	0.36 (0.51)	0.31 (0.44)	0.26 (0.37)

TABLE 5 Prevalence of exposure to valproate in the pregnancy cohort between 2015 and 2021 and mean (SD) prevalence before and after the introduction of the pregnancy prevention program in Switzerland in 2018. Weighted numbers (including methodology) are shown in Table S4 to increase comparability to a previous study evaluating the prevalence of exposure to valproate in Switzerland.

Systemic glucocorticoids accounted for 75% of all claimed teratogens during the first trimester, 72% during the preconceptional period, and 56% of all claimed teratogens in women of childbearing age. Systemic glucocorticoids have been used during pregnancy for many decades. Despite a long-debated potential association with an increased risk of cleft lip that was not confirmed in more recent studies,[14] systemic glucocorticoids often remain the drug of choice if immunosuppression or a rapid anti-inflammatory effect is required during pregnancy, due to a paucity of sufficiently investigated safe and/or equally effective alternatives. Recent literature further suggests that not all systemic glucocorticoids cross the placenta (mainly betamethasone and dexamethasone cross the placenta effectively).[15] In Germany, exposure prevalence to systemic glucocorticoids during the first trimester (62/10 000) was lower compared to our study (103.8/10 000 pregnancies), whereas exposure to most other potential teratogens was similar.[1] The reason for this difference remains unclear, as systemic glucocorticoids are reimbursed by health insurance in both countries.

The second and third most prevalent teratogens during the first trimester were also weak teratogens. The antibiotic trimethoprim in combination with sulfamethoxazole (cotrimoxazol) accounted for 10.2% of all claimed potential teratogens. In Switzerland, cotrimoxazol is not a first-line treatment option, but may be used short-term if treatment of choice is not effective. Trimethoprim and sulfamethoxazole inhibit folic acid.[16] Animal studies have shown potential teratogenicity for folic acid inhibitors, and a potentially slightly increased risk of neural tube defects, malformations of the heart, urinary tract, and cleft lip, but studies in humans have found this risk to be small.[16] The combined thyreostatic thiazamole/carbimazole was claimed by 2.3%, and has been specifically associated with cutis aplasia, choanal atresia, esophageal atresia, facial dysmorphia, abdominal wall defects, and nipple hypo/aplasia.[17–19] The American Thyroid Association recommends propylthiouracil over carbimazole during the preconceptional period and first trimester,[20] but studies on the risk of malformations in association with propylthiouracil have also shown conflicting results.[21–23]

The three ASMs topiramate, carbamazepine, and valproate ranked position 4–6 of the most prevalent teratogens during the first trimester, and together accounted for 4.8% of all claimed teratogens. First trimester exposure to topiramate (2.6/10 000 in our study), which is predominantly used to prevent migraines, has been repeatedly associated with a five-fold increased risk of cleft lip and palate.[24] Given that exposure to topiramate was higher among women of childbearing age (20.1/10 000 women) and during the preconceptional period (5.5/10 000), practitioners seem to be aware of the teratogenic risk of topiramate and the fact that safer antimigraine treatments are usually available. First trimester exposure to carbamazepine doubles the risk of various malformations (to approximately six malformations per 100 births), but carbamazepine is a potent seizure prevention and can be the ASM of choice when safer options such as lamotrigine are not sufficiently effective, because other potent ASM such as valproate are significantly more teratogenic.[24] This is also reflected by the fact that exposure prevalence to carbamazepine was more similar between women of childbearing age (3.6/10 000), during the preconceptional period (3.2/10 000), and during the first trimester (2.6/10 000) compared to topiramate. Uncontrolled epilepsy during pregnancy usually represents a greater risk for mother and child than therapy with carbamazepine.[24]

Valproate was the most frequently used unequivocally potent teratogen during the first trimester in our study (1.4/10 000 women) and in Germany (2/10 000 women).[1] Approximately 11% of children with *in utero* exposure to valproate in the first trimester are born with structural MCM. In addition, exposure to valproate later during pregnancy causes neurodevelopmental disorders in 30–40% of children.[24] Reassuringly, our results suggest that the use of valproate during the first trimester more than halved after the introduction of a pregnancy prevention program in December 2018 in Switzerland.[11] However, future studies based on other data sources and including data past 2021 should evaluate if this positive development continues and if results can be confirmed in larger sample sizes. For example, including data from other Swiss health insurances would strengthen the evidence, and a larger number of events would enable the possibility of conducting more advanced analyses, such as time series analyses.

In women of childbearing age, exposure to weak and proven teratogens increased with age, likely reflecting a higher prevalence of

chronic diseases and drug use in general as well as more frequent pregnancy complications with increasing age. On the other hand, exposure to unequivocally potent teratogens was highest among women <26 years, which was exclusively due to exposure to systemic isotretinoin (acne therapeutic). Systemic retinoids cause MCM in up to 50% of first trimester exposures.[1] Recorded claims of systemic isotretinoin during the first trimester (0.9% of all claimed teratogens) need to be interpreted cautiously, given that LMP in our study had to be estimated and may not be exact for every pregnancy. However, our results show that a meaningful number of women claim systemic isotretinoin close to the date of conception (34 women in the 90-day preconceptional period). Compared to Germany, the use of systemic isotretinoin among women aged <26 years was almost 4.5-fold higher in the Helsana database (0.80% vs. 0.18% in Germany).[1] Given that systemic isotretinoin preparations are reimbursed in both countries, differential measurement of drug use does not explain this finding. Moreover, official pregnancy prevention programs are in place in both countries.[25,26] Demographic differences between the collectives of insured patients might account for a small part of this discrepancy, but the relatively high dispensation rate of systemic isotretinoin in Switzerland should be further investigated in follow-up studies and the risk associated with pregnancy should be communicated.

This study has the following limitations. First, Swiss claims data did not allow the inclusion of pregnancies which ended in termination or abortion before gestational week 22. Abortions and miscarriages are only recorded in Swiss claims data if a medical intervention (i.e., DNC or misoprostol application) was undertaken, whereas miscarriages without an intervention are not recorded. Moreover, the gestational length, and thus the potential window of teratogen exposure, of these miscarriages/abortions is unknown. Thus, our prevalence of exposure to teratogens during pregnancy may be underestimated especially for potential teratogens which may lead to premature fetal death. Second, we were not able to evaluate the indication for the use of drugs in this study, because diagnosis codes are not recorded in our data. Thus, we could not evaluate whether exposure to potential teratogens during the first trimester was clinically indicated or not. Using extrapolation methods and prevalence of disease data, a prior study based on Helsana data has estimated that valproate was likely claimed more frequently than clinically indicated for seizure prevention between 2014 and 2018.[6] Third, we were not able to evaluate the occurrence of MCM in children exposed to teratogens, because all costs associated with birth defects are covered by a separate governmental disability insurance in Switzerland and are thus not captured in data of health insurance such as Helsana. Legal uncertainties and privacy concerns have hampered many efforts to link different data sources in Switzerland in the past. Fourth, results are based on 5.6% of all completed pregnancies in Switzerland during this time period and may not be entirely representative of the overall Swiss population in terms of baseline characteristics.[27,28] It is further possible that the requirement of continuous insurance throughout the observation period might have resulted in an overrepresentation of women with a higher socioeconomic status, because women facing greater financial constraints may more frequently change health insurance. Fifth, seasonality may influence the use of the antibiotic trimethoprim/sulfamethoxazole among women of childbearing age, which is not the case for other studied medications. Sixth, we do not know whether claimed medications were taken. Lastly, it is possible that we slightly underestimated the exposure prevalence to teratogens as our sensitivity analysis in 270-day periods tended to result in higher proportions of exposed women. This affects the exposure prevalence of short-term treatments (e.g., systemic glucocorticoids).

5 | CONCLUSION

Most medications with teratogenic effects debated or proven dispensed to women of childbearing age and pregnant women (during preconception and the first trimester) were in the group of weak teratogenicity level. This study further indicates that exposure to proven and unequivocally potent teratogens during pregnancy is much lower during the first trimester compared to the time before pregnancy and among women of childbearing age. Claims for valproate dropped by ≥50% following the introduction of the pregnancy prevention program in 2018, but the sample size was small.

AUTHOR CONTRIBUTIONS

Carole A. Marxer: conceptualization, data curation, formal analysis, investigation, methodology, project administration, software, visualization, writing – original draft preparation, writing – review and editing. **Sereina M. Graber:** conceptualization, data curation, formal analysis, investigation, methodology, validation, writing – review and editing. **Daniel Surbek** and **Alice Panchaud:** conceptualization, investigation, methodology, validation, writing – review and editing. **Christoph R. Meier:** conceptualization, funding acquisition, project administration, resources, supervision, validation, writing – review and editing. **Julia Spoendlin:** conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, software, supervision, validation, visualization, writing – original draft preparation, writing – review and editing.

ACKNOWLEDGMENTS

We thank the Helsana Insurance Group for providing the data. We further thank the Freiwillige Akademische Gesellschaft (FAG) Basel for financially supporting the participation and poster presentation at the 39th International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE 2023, travel fund). We further thank Dr. Veronika Lappe (PMV Research Group, University of Cologne, Faculty of Medicine and University Hospital Cologne (AöR)) for providing the ATC codes of the teratogens and for valuable exchange regarding the comparability of our results with results presented in the 2021 Annual BARMER drug report[1] in which Dr. Veronika Lappe contributed as an author.

CONFLICT OF INTEREST STATEMENT

None.

ETHICS STATEMENT

This retrospective observational study using anonymous data did not require an ethics committee approval. Patient consent was waived due to using anonymous data.

ORCID

Carole A. Marxer https://orcid.org/0000-0002-4688-8223
Daniel Surbek https://orcid.org/0000-0001-7705-1584
Alice Panchaud https://orcid.org/0000-0001-6086-2401
Christoph R. Meier https://orcid.org/0000-0002-7120-6378
Julia Spoendlin https://orcid.org/0000-0003-1632-1928

REFERENCES

1. Grandt D, Lappe V, Schubert I. BARMER Arzneimittelreport 2021. [Barmer Drug report 2021] In German. 41 p. 2021, Berlin, BARMER Institut für Gesundheitssystemforschung (BIFG).
2. Koopman P. *Organogenesis in Development*. 1st ed. 456 p. Elsevier; 2010.
3. Centers for Disease Control and Prevention. Unintended pregnancy. 2023. https://www.cdc.gov/reproductivehealth/contraception/unintendedpregnancy/index.htm. Accessed May 25, 2023.
4. Gerbier E, Graber SM, Rauch M, et al. Use of drugs to treat symptoms and acute conditions during pregnancy in outpatient care in Switzerland between 2014 and 2018: analysis of Swiss healthcare claims data. *Swiss Med Wkly*. 2021;151:w30048.
5. Gerbier E, Graber SM, Rauch M, et al. Use of prescribed drugs to treat chronic diseases during pregnancy in outpatient care in Switzerland between 2014 and 2018: descriptive analysis of Swiss health care claims data. *Int J Environ Res Public Health*. 2022;19:1456.
6. Spoendlin J, Blozik E, Graber S, et al. Use of valproate in pregnancy and in women of childbearing age between 2014 and 2018 in Switzerland: a retrospective analysis of Swiss healthcare claims data. *Swiss Med Wkly*. 2021;151:w20386.
7. Dathe K, Schaefer C. The use of medication in pregnancy. *Dtsch Arztebl Int*. 2019;116:783-790.
8. Marxer CA, Graber SM, Surbek D, Panchaud A, Meier CR, Spoendlin J. Dispensed drugs during pregnancy in outpatient care between 2015 and 2021 in Switzerland: a retrospective analysis of Swiss healthcare claims data. *Swiss Med Wkly*. 2024;154:3616.
9. MacDonald SC, Cohen JM, Panchaud A, McElrath TF, Huybrechts KF, Hernández-Díaz S. Identifying pregnancies in insurance claims data: methods and application to retinoid teratogenic surveillance. *Pharmacoepidemiol Drug Saf*. 2019;28:1211-1221.
10. Margulis AV, Setoguchi S, Mittleman MA, Glynn RJ, Dormuth CR, Hernandez-Diaz S. Algorithms to estimate the beginning of pregnancy in administrative databases. *Pharmacoepidemiol Drug Saf*. 2013;22:16-24.
11. Swissmedic (Schweizerisches Heilmittelinstitut). DHPC – Valproat (Depakine®, Depakine Chrono®, Valproate Chrono Sanofi®, Orfiril®, Valproat Chrono Desitin®, Valproat Sandoz®, Convulex®). 2018. https://www.swissmedic.ch/swissmedic/de/home/humanarzneimittel/marktueberwachung/health-professional-communication--hpc-/dhpc-valproat_depakine-depakine_chrono_valproate_chrono_sanofi.html. Accessed October 20, 2023.
12. Van Rossum G, Drake FL. *Python 3 Reference Manual*. CreateSpace; 2009.
13. Federal Statistical Office. Durchschnittsalter von Müttern und Vätern bei Geburt des Kindes nach Staatsangehörigkeitskategorie, 1971–2021 [Average age of mothers and fathers at birth of the child by citizenship category, 1971–2021] in German. 2022. https://www.bfs.admin.ch/bfs/de/home/statistiken/bevoelkerung/geburten-todesfaelle/fruchtbarkeit.assetdetail.23328885.html. Accessed March 6, 2023.
14. Embryotox. Prednisolon. 2023. https://www.embryotox.de/arzneimittel/details/ansicht/medikament/prednisolon. Accessed October 20, 2023.
15. Briggs GG, Freeman RK, Tower CV. *Brigg's Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*. 12th ed. Lippincott Williams & Wilkins (LWW); 2021.
16. Embryotox. Co-trimoxazol. 2023. https://www.embryotox.de/arzneimittel/details/ansicht/medikament/co-trimoxazol/. Accessed October 20, 2023.
17. CRAT. Carbimazole/Thiamazole. 2021. https://www.le-crat.fr/spip.php?page=article&id_article=296#:~:text=On préfèrera utiliser le propylthiouracile,environ 20 mg de thiamazole. Accessed October 20, 2023.
18. Embryotox. Thiamazol. 2023. https://www.embryotox.de/arzneimittel/details/ansicht/medikament/thiamazol/Accessed October 20, 2020.
19. Embryotox. Carbimazol. 2023. https://www.embryotox.de/arzneimittel/details/ansicht/medikament/carbimazol/. Accessed October 20, 2023.
20. Alexander EK, Pearce EN, Brent GA, et al. 2017 guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the postpartum. *Thyroid*. 2017;27:315-389.
21. Andersen SL, Lönn S, Vestergaard P, Törring O. Birth defects after use of antithyroid drugs in early pregnancy: a Swedish nationwide study. *Eur J Endocrinol*. 2017;177:369-378.
22. Andersen SL, Olsen J, Sen WC, Laurberg P. Birth defects after early pregnancy use of antithyroid drugs: a Danish Nationwide study. *J Clin Endocrinol Metab*. 2013;2023(98):4373-4381.
23. Song R, Lin H, Chen Y, Zhang X, Feng W. Effects of methimazole and propylthiouracil exposure during pregnancy on the risk of neonatal congenital malformations: a meta-analysis. *PLoS One*. 2017;2023(12):e0180108.
24. Marxer CA, Rüegg S, Rauch MS, Panchaud A, Meier CR, Spoendlin J. A review of the evidence on the risk of congenital malformations and neurodevelopmental disorders in association with antiseizure medications during pregnancy. *Expert Opin Drug Saf*. 2021;20:1487-1499.
25. Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM). Retinoide: Aktualisierte Maßnahmen zur Schwangerschaftsverhütung sowie Warnhinweise zu neuropsychiatrischen Erkrankungen bei oraler Anwendung [Retinoids: Updated contraceptive measures and warnings on neuropsychiatric disorders with oral use].Accessed July 8, 2022. https://www.bfarm.de/SharedDocs/Risikoinformationen/Pharmakovigilanz/DE/RV_STP/m-r/retinoide.html#:~:text=Das Schwangerschaftsverhütungsprogramm für Acitretin%2C Alitretinoin,und nach der Behandlung anzuwenden
26. Swissmedic (Schweizerisches Heilmittelinstitut). HPC – Die sichere Anwendung von Retinoiden in der Dermatologie [HPC – The safe use of retinoids in dermatology]. 2017. https://www.swissmedic.ch/swissmedic/de/home/humanarzneimittel/marktueberwachung/health-professional-communication--hpc-/archiv/hpc-_-die-sichere-anwendung-von-retinoiden-in-der-dermatologie.html. Accessed October 20, 2020.
27. Federal Statistical Office. Births. 2022. https://www.bfs.admin.ch/bfs/en/home/statistics/population/births-deaths/births.html. Accessed March 6, 2023.
28. Federal Statistical Office. Anzahl Todesfälle und rate der perinatalen, Säuglings- und Kindersterblichkeit [Number of deaths and rate of

perinatal, infant and child mortality]. 2022. https://www.bfs.admin.ch/bfs/en/home/statistics/health/state-health/mortality-causes-death/infant-stillbirths.assetdetail.23329947.html. Accessed March 6, 2023.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Marxer CA, Graber SM, Surbek D, Panchaud A, Meier CR, Spoendlin J. Exposure to potentially teratogenic medications before and during the first trimester of pregnancy compared to women of childbearing age: A retrospective analysis of Swiss claims data (2015–2021). *Acta Obstet Gynecol Scand*. 2025;00:1-13. doi:10.1111/aogs.15052