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Queries on medication use during pregnancy: characterisation of the Swiss Teratogen Information Service database

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Summary

AIMS OF THE STUDY: Limited information on medication safety may result in concerns on how to treat pregnant and breast-feeding patients. The Swiss Teratogen Information Service (STIS) provides information to healthcare professionals about medications during pregnancy and breast feeding. Our objective was to describe the queries addressed to the STIS over the past two decades.

METH ODS: The STIS maintains a database of queries on pregnancy outcomes after exposure to various substances, which may be a valuable source of information. We initially analysed the general characteristics of all queries. Thereafter, we focused on exposure to medications during singleton pregnancies and associated health-related aspects.

RESULTS: From 2000 to 2019, 7148 queries were entered into the database. An increasing number of queries was recorded over the study period, with an average of 357 queries entered into the database per year. Most of the enquirers were physicians; more specifically, gynaecologists/obstetricians (2389/7148; 33.4%) and psychiatrists (1007/7148; 14.1%). Two thirds (4747/7148; 66.4%) of the queries addressed medication intake during pregnancy; the next most frequent queries concerned planned medication in the context of pregnancy (928/7148; 13.0%) or medication use during breast-feeding (873/7148; 12.2%). In more than 50% (3611/7148) of cases, women were treated with more than one drug; altogether, 15193 medications (taken alone or in combination) were identified. The most frequent queries concerned medicines for the nervous system (ATC group N, n = 7042), with selective serotonin reuptake inhibitors (n = 1271) in the leading position, followed by benzodiazepine derivatives (n = 1102) and other antidepressants (n = 780). The next most frequently mentioned drug classes were anti-infectives for systemic use (J, n = 1586) and drugs for the alimentary tract and metabolism (A, n = 1205). Analysis of follow-up information on cases of medication exposure during singleton pregnancies (n = 2672) revealed an offspring malformation rate of 4.2%. The organ system most often affected was the musculoskeletal system, followed by the circulatory system; congenital malformations of the nervous system and chromosomal abnormalities were also seen. The three most frequently documented congenital diagnoses were malformations of cardiac septa, the brain and major arteries.

CONCLUSIONS: Healthcare professionals often have concerns regarding the treatment of pregnant women with medication, and require professional counselling in this area. A variety of drugs are mentioned in queries addressed to the STIS, of which psycholeptics and psychoanaleptics are the most frequent. Proper guidelines on their use during pregnancy appear particularly urgent.

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Introduction

For several reasons, the evidence level for most treatments during pregnancy is low. Pregnant women are usually excluded from clinical trials conducted outside the field of obstetrics (see e.g., [1]). Given the changes in metabolism and physiology that take place during pregnancy, this means that the results of existing clinical trials only partially apply to the pregnancy period. Moreover, evidence on adverse effects on the embryo/fetus – typically obtained in postmarketing studies – is usually scarce. These aspects severely reduce the number of medications labelled for use during pregnancy [2]. In the absence of clear, established recommendations, both healthcare professionals and patients often feel unsure about this topic. Fear of teratogenic effects on unborn children seems to be widespread. Also, the existence of a background rate of major malformations with undefined origin (in Europe close to 2.6% [3]) probably plays a role in the persistence of this fear. In Switzerland, physicians and pharmacists routinely overestimate the risks generated by drug intake during pregnancy [4], whereas pregnant women often try to reduce medication consumption themselves [5, 6].

The Swiss Teratogen Information Service (STIS), which is situated at the Lausanne University Hospital (CHUV) as

part of the department of clinical pharmacology, is dedicated to providing healthcare professionals evidence-based information on drug safety issues during pregnancy and breastfeeding. Healthcare professionals contact the STIS with specific queries, and the information collected on the corresponding cases is entered into a database. This study aimed to provide an overview of the queries addressed to the STIS over the past two decades. After an initial general characterisation of the queries and enquirers, we took a closer look at the medication exposures that occur during pregnancy and their clinical follow-up, including offspring outcome.

Materials and methods

Study design and the Swiss Teratogen Information Service (STIS) database

In this descriptive study, variables available from the STIS database were analysed. In part 1 of the study, we analysed the general characteristics of all case-specific queries (i.e., queries on general, non-case-specific aspects were not considered). In part 2, we focused on exposures to medications during pregnancy and associated health-related aspects of mothers and their offspring. Here, only queries with a focus on treatment adjustments or effects during singleton pregnancies and with follow-up information (available for 72% of the queries; data not shown) were considered.

Queries on exposure to medications and other substances can be addressed to the STIS by telephone, e-mail or an online referral form. The STIS answers the queries with expert evidence-based information, free of charge. Medications are documented by using the Anatomical Therapeutic Chemical (ATC) classification system. If there are maternal diagnoses or any neonatal malformations or symptoms, these are documented using the 10th revision of the International Statistical Classification of Diseases (ICD-10) system.

Part 1: general characterisation of queries

For all queries, the following information is routinely collected and entered into the STIS-database: type of enquirer, focus of the query (treatment adjustment/effects or causality assessment), circumstances of the query (whether it took place during pregnancy, during pregnancy planning, etc.), and demographic and health-related data of the mothers (compare with [7]). Information on circumstances and focus of the queries as well as on the type of enquirer are entered into the STIS database in a standardised way and were analysed as such. With the exception of folic acid, where a closed question is included, all other medications are to be listed by the enquirer, with extra spaces for dosage, period of use and route of administration. The following risk factors and comorbidities are recorded systematically: alcohol, tobacco and illicit drug use, hypertension, diabetes, obesity, history of congenital anomaly and risk related to psycho-social context. Enquirers are also given the opportunity to list other comorbidities as free text.

To determine from which canton a query came, we assigned the canton name to each available postal code. For longitudinal comparisons, the total time period of 20 years was divided into blocks of 5 years each. For medication analyses, we shortened the given ATC codes to the first level (anatomical main group), second level (therapeutic subgroup) and fourth level (chemical subgroup). Our analysis took into account all medications taken by the patients and was not limited to the specific medication asked about in the query. Vitamins (ATC codes A11A, A11B, A11H and A11J), oral iron (ATC codes B03AA, B03AB, B03AD and B03AE), minerals and supplements (ATC Code A12) and general nutrients (ATC Code V06) as well as chemicals and illicit and recreational drugs (ATC Code V07A) were excluded in a later step.

Part 2: analysis of follow-up information

Follow-up pregnancy outcome information is collected via postal questionnaire, which is sent to the initial enquirer at first contact and shortly after the expected date of delivery. Information reported on medication and comorbidities at first contact can be confirmed when providing pregnancy outcome information. In cases of non-response, one reminder is sent systematically. Outcomes not returned to the service 18 months after the estimated date of delivery are considered lost to follow-up. Follow-up information on the following pregnancy outcomes is recorded systematically: spontaneous abortion, elective termination of pregnancy, live birth, date of end of pregnancy, and gender, birth weight, length and head circumference of the child. Comments on obstetric outcomes and malformations can be provided as free text by the enquirer.

Multiple pregnancies were identified by search of related terms in the free text fields and excluded (see appendix). Analyses required information on pregnancy trimesters. These were defined according to the classification of the ConcePTION project (s. https://www.imi-conception.eu/): the first trimester was classified as date of last menstrual period (LMP) to LMP + 90 days, the second trimester as LMP + 91 days to LMP + 188 days, and the third trimester as LMP + 189 days to birth.

Maternal, obstetric and neonatal diagnoses were analysed separately. ICD-10 codes were used at chapter level (one-character codes) and at category level (three-character codes). Mothers and children in cases with no specifically recorded ICD-10 codes were assumed to be healthy. Data on obstetric diagnoses (ICD-10 chapter O) were extracted from information in the queries as well as from follow-up. Diagnoses mentioned in the follow-up were checked manually, so that codes concerning non-pregnancy-related maternal diagnoses could be assigned to the maternal comorbidities. The term miscarriage was defined as the death of a fetus ≤153 days after LMP, which corresponds to the 22nd completed week of pregnancy. Intrauterine death of a fetus after this time was classified as stillbirth.

Documentation of the mother's risk factors, such as tobacco consumption, obesity or hypertension, changed slightly during the two decades of query documentation. Whereas in earlier years they were assigned an ICD-10 code, from 2014 onwards they were recorded directly as communicated (e.g., tobacco consumption yes/no). To facilitate analysis, we coded those risk factors into ICD-10 codes a posteriori. In addition, codes for tobacco, alcohol or drug use or dependence (F10–F19) were converted into codes indicating substance consumption in general (Z72.0, Z72.1 and Z72.2). Risk factors summarised under "psychosocial con-

dition" and "congenital condition in the family" were not assigned to an ICD-10 code.

Information on pregnancy outcome was classified by combining data on abortions (both spontaneous and medical), stillbirths and other pregnancy outcomes (named "others", e. g., ectopic pregnancies) [8]. For all cases without a specific code, a live birth was assumed. Children's outcomes were coded with ICD-10. EUROCAT guidelines [9] were used as a reference for definition and description of minor and major congenital anomalies.

Data analysis

Data on multiple variables from the database – obtained during the initial query and when available also from the corresponding follow-up – were exported into an Excel table that was sent from the STIS to the University Hospital of Zurich on 28 September 2020 and constituted the basis for the present study. Descriptive statistics of all variables were derived using the program "Microsoft Excel" version 16. Standardised database variables were analysed with "IBM SPSS Statistics" version 27. Data are shown as numbers and percentages. No detailed study protocol was prepared before starting with the analysis.

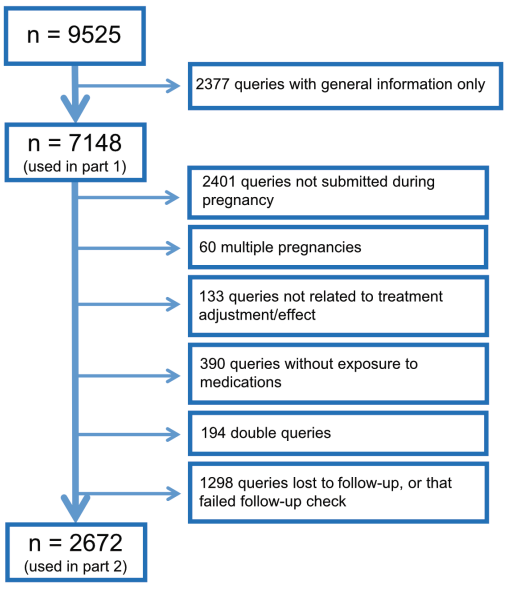
Ethics statement

This retrospective analysis of anonymised data was conducted in compliance with Swiss Federal Law on data protection (Human Research Act, Article 2) and does not require ethics committee approval or informed consent [10].

Results

Overall, 9525 queries were submitted to the STIS between 1 January 2000 and 31 December 2019 (fig. 1). Of these, 2377 contained information of a more general nature only and were excluded from the present analysis.

Figure 1: Queries flow chart used to obtain sample analysed in parts 1 and 2.



Part 1: general characterisation of queries

Sociodemographic information

From 2000 to 2019, 7148 queries were entered into the STIS database. This corresponds to an average of 357 queries recorded per year, although the number of queries steadily increased over the years. The main enquirers were physicians, with a majority of gynaecologists/obstetricians and psychiatrists (table 1).

Data on the type of enquirer has been available only since 2009, resulting in a high number of cases with missing information on the enquirers.

Half of the requests came from the canton of Vaud, where the STIS is situated. In addition, the STIS received calls from all the French-speaking cantons of Switzerland as well as from the biggest, often university-associated German speaking cantons and the Italian-speaking canton Ticino. In 2.8% of the cases, the origin of the query was missing.

Table 1:
Characterisation of the queries addressed to the STIS between 2000 and 2019 (n = 7148).

Time period	Number	Percentage (%)
2000 to 2004	1452	20.3
2005 to 2009	1495	20.9
2010 to 2014	2011	28.1
2015 to 2019	2190	30.6
Enquirers		
Gynaecologist/obstetrician	2389	33.4
Psychiatrist	1007	14.1
MD other speciality	337	4.7
General practitioner	226	3.2
Paediatrician	170	2.4
Midwife	92	1.3
Pharmacy	70	1.0
Patient/relatives/partner	49	0.7
Missing	2808	39.3
Geographical origin (canton)		
Vaud	3514	49.2
Neuchâtel	660	9.2
Zurich	548	7.7
Valais	392	5.5
Ticino	324	4.5
Bern	276	3.9
Fribourg	275	3.8
Geneva	232	3.2
Basel	199	2.8
Aargau	157	2.2
Jura	81	1.1
Others	288	4.0
Missing	202	2.8
Circumstance of query		
During pregnancy	4747	66.4
Planning of a pregnancy or of a drug treatment during pregnancy	928	13.0
During breastfeeding	873	12.2
Pre- or periconceptional	414	5.8
Related to the father	178	2.5
Missing	8	0.1
Focus of query		
Treatment adjustment or effect	6976	97.6
Causality assessment	172	2.4

Circumstances and focus of the queries

In two thirds of the cases, queries were submitted to the STIS during an ongoing pregnancy. Other circumstances included the planning of a pregnancy or of a drug treatment during pregnancy, drug treatment during breast-feeding, pre- or periconceptional exposures and paternal exposures. Most (97.6%) of the questions were anticipatory, with emphasis on treatment adjustments or effects. In 2.4% of the cases, the query was submitted retrospectively, focusing on causality assessment.

Medications

After exclusion of vitamins, minerals, supplements, general nutrients, as well as chemicals and illicit or recreational drugs, a total of 15193 medications were mentioned in the queries and documented by the STIS (fig. 2).

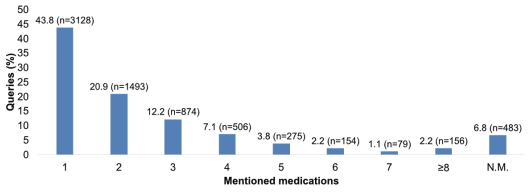
In 50.5% of the queries (n = 3611/7148), women were taking more than one medication. The results depicted in figure 3A show that medications for the nervous system (46.4%) were the most commonly mentioned class of drugs, followed by anti-infectives for systemic use (10.4%) and medications for the alimentary tract and metabolism (7.9%).

The longitudinal analysis of medications showed that the medications for the nervous system were the most frequently mentioned drug class in all four time periods, rising from 5.8% in 2000–2004 to 16.2% in 2015–2019 (fig. 3B). Anti-infectives were superseded by drugs for the alimentary tract and metabolism in the time period 2015–2019 (2.5% versus 2.9%, respectively). The number of antineoplastic and immunomodulating agents increased notably over time (from 0.7% in 2000–2004 to 2.3% in 2015–2019). The other substance classes never reached 2% of the total number of medications over the years considered.

The therapeutic subgroup most often mentioned within the drug class for the nervous system (fig. 4A) was psycholeptics, followed by psychoanaleptics, analgesics, antiepileptics and anaesthetics.

The chemical subgroups were dominated by selective serotonin reuptake inhibitors, benzodiazepine derivatives and other antidepressants. The therapeutic subgroup most often mentioned within the class of the anti-infectives for systemic use (fig. 4B) was antibacterials, followed by vaccines, antivirals, antimycobacterials, antimycotics, and immune sera and immunoglobulins. Fluoroquinolones were the most frequently seen anti-infectives, followed by tetracyclines and macrolides.

Figure 2: Number of medications mentioned in queries to the STIS from 2000 to 2019 (n = 7148). Note that vitamins, minerals, oral iron, chemicals and illicit/recreational drugs were not considered. N.M., not medication-related (e.g., radiological examinations, chemical exposures or illicit/recreational drug exposures)



Part 2: analysis of follow-up information

Since only queries with a focus on treatment adjustments or effects during singleton pregnancies with follow-up information on the offspring were considered, cases without any exposure to medications (n = 390; e. g., cases with exposures to illicit or recreational drugs only or radiological examinations) as well as cases with more than one query during the same pregnancy (n = 194) were excluded. Cases with no follow-up or that did not reach the quality standard of our manual follow-up check (e. g., cases with very little information in the follow-up or patients who did not take treatment or were not pregnant after all, n = 1298) were also excluded, resulting in a total of 2672 cases available for analysis. A total of 6583 medications were mentioned in these queries. Their distribution among the various classes was very similar to that described above (part 1), with only a few minor changes; the exact data can be seen in supplementary figures S1 and S2 in the appendix.

Figure 3: Medications mentioned in the queries to the STIS from 2000 to 2019. The total number of medications was 15193; vitamins, minerals, oral iron, chemicals and illicit/recreational drugs were not considered. Frequency of the various anatomical main groups is shown in total (A) or per period (B). B, given the high percentage of drugs for the nervous system (N), the y-axis is shown in a broken scale; data on the various anatomical main groups in the four different time periods are shown as percentages of all medications mentioned in the queries from 2000 to 2019 (if >2%). * excluding sex hormones and insulins

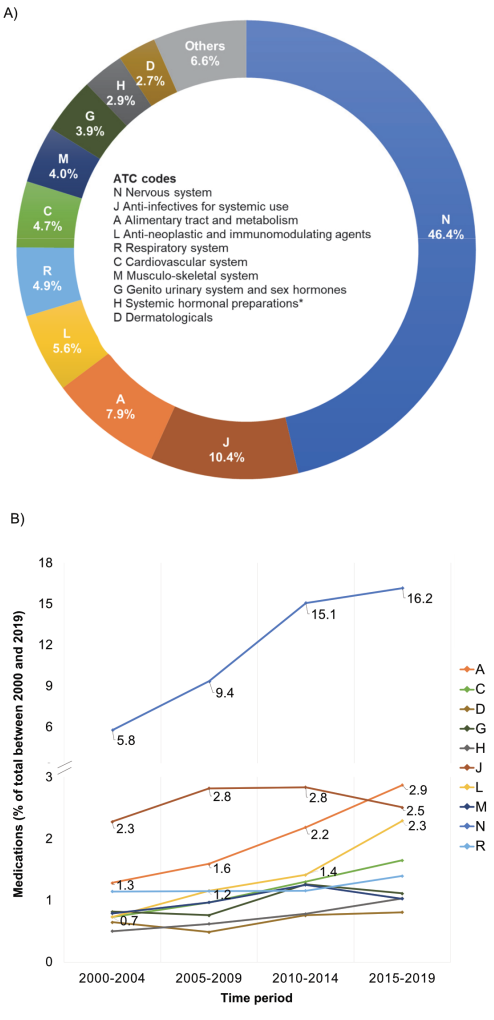
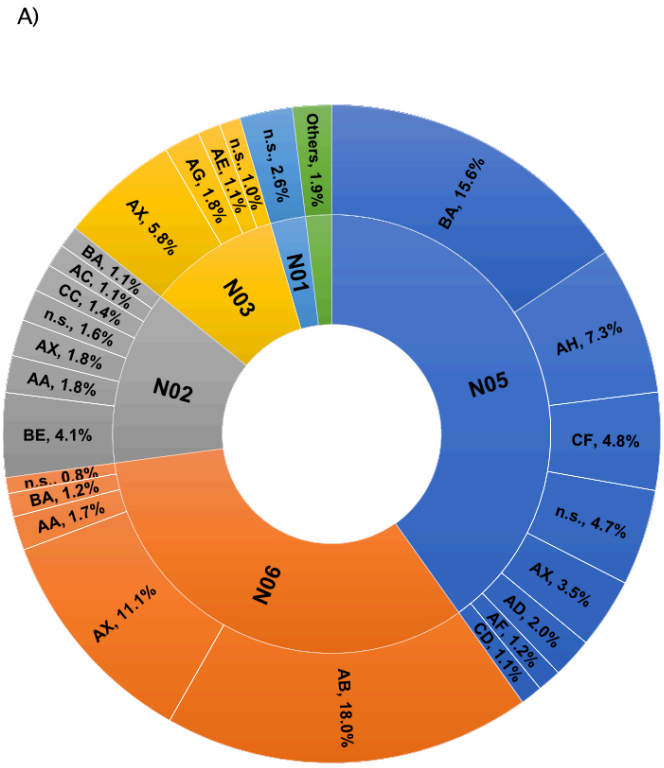
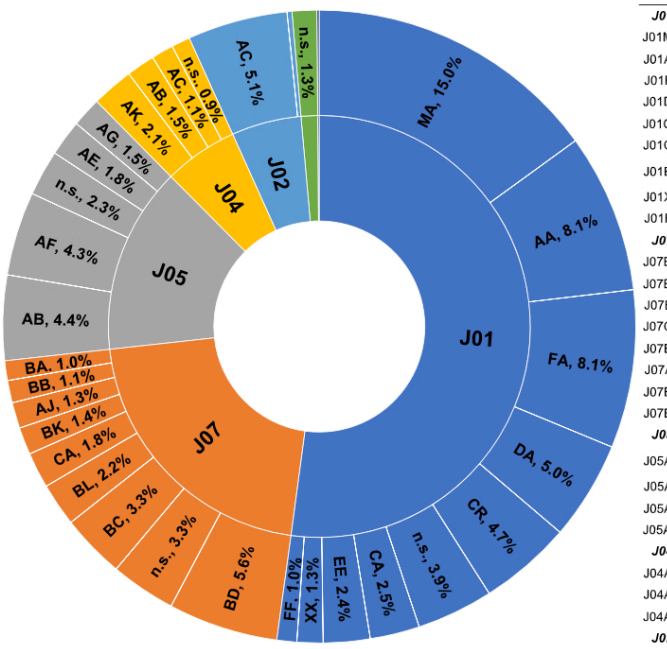


Figure 4: Medications for the nervous system (A, anatomical main group N; n = 7042) and anti-infectives for systemic use (B, anatomical main group J; n = 1586) mentioned in the queries to the STIS. The light green sector "Others" in A is not labelled owing to its small size. The same applies to the light green sector "J06" in B. The subsector "n.s." from the therapeutic subgroup "J02" and the sector "Others" in B are not labelled owing to their small size; they amount to 0.3% and 0.1%, respectively.



Codes	Description
N05	***Psycholeptics***
N05BA	Benzodiazepine derivatives
N05AH	Diazepines, oxazepines, thiazepines and oxepines
N05CF	Benzodiazepine related drugs
N05AX	Other antipsychotics
N05AD	Butyrophenone derivatives
N05AF	Thioxanthene derivatives
N05CD	Benzodiazepine derivatives
N06	***Psychoanaleptics***
N06AB	Selective serotonin reuptake inhibitors
N06AX	Other antidepressants
N06AA	Non-selective monoamine reuptake inhibitors
N06BA	Centrally acting sympathomimetics
N02	***Analgesics***
N02BE	Anilides
N02AA	Natural opium alkaloids
N02AX	Other opioids
N02CC	Selective serotonin (5HT1) agonists
N02AC	Diphenylpropylamine derivatives
N02BA	Salicylic acid and derivatives
N03	***Antiepileptics***
N03AX	Other antiepileptics
N03AG	Fatty acid derivatives
N03AE	Benzodiazepine derivatives
N01	***Anesthetics***
n.s.	not specified



Codes	Description
J01	***Antibacterials***
J01MA	Fluoroquinolones
J01AA	Tetracyclines
J01FA	Macrolides
J01DA	Cephalosporins
J01CR	Combinations of penicillins, incl. beta-lactamase inhibitors
J01CA	Penicillins with extended spectrum
J01EE	Combinations of sulfonamides and trimethoprim, incl. derivatives
J01XX	Other antibacterials
J01FF	Lincosamides
J07	***Vaccines***
J07BD	Measles vaccines
J07BC	Hepatitis vaccines
J07BL	Yellow fever vaccines
J07CA	Bacterial and viral vaccines, combined
J07BK	Varicella zoster vaccines
J07AJ	Pertussis vaccines
J07BB	Influenza vaccines
J07BA	Encephalitis vaccines
J05	***Antivirals***
J05AB	Nucleosides and nucleotides excl. reverse transcriptase inhibitors
J05AF	Nucleoside and nucleotide reverse transcriptase inhibitors
J05AE	Protease inhibitors
J05AG	Non-nucleoside reverse transcriptase inhibitors
J04	***Antimycobacterials***
J04AK	Other drugs for treatment of tuberculosis
J04AB	Antibiotics
J04AC	Hydrazides
J02	***Antimycotics***
J02AC	Triazole derivatives
J06	***Immune sera and immunoglobulins***
n.s.	not specified

Maternal health-related characteristics, including obstetric outcomes

The average age of the mothers was 31.3 ± 5.8 years (average ± standard deviation; median, 32 years; minimum, 14 years; maximum, 48 years; table 2).

In the majority of the cases, the query was submitted in the first trimester. In total, 2233 maternal comorbidities and 667 risk factors had been recorded in the database. The groups of diagnoses most often reported were mental and behavioural disorders (ICD-10 chapter V; F-diagnoses), endocrine, nutritional and metabolic diseases (chapter IV; E) and diseases of the nervous system (chapter VI; G). Depressive episodes (F32), obesity (E66) and other anxiety disorders (F41) occupied the three highest ranks of the diagnoses (fig. 5).

The consumption of recreational or illicit substances was the most frequently documented risk factor. Further risk factors were psychosocial conditions in general and congenital conditions in the family. The three most frequent obstetric outcomes were diabetes mellitus in pregnancy (O24), preterm labour and delivery (O60) and pre-eclampsia (O14) (table 3).

Pregnancy outcome

Overall, 2240 diagnoses related to pregnancy outcomes were documented (including live births and abortions). The analysis revealed the occurrence of live births in 80.4% of the cases, abortions (medical or spontaneous) in 18.8%, stillbirths in 0.5% and others in 0.3% of the cases; see supplementary table S1 in the appendix. A total of 670 ICD-10 diagnoses concerning the perinatal and neonatal outcome of the children were found. As shown in figure 6, the most frequently mentioned groups of diagnoses were conditions originating in the perinatal period (chapter XVI; P), congenital malformations, deformations and chromosomal abnormalities (chapter XVII; Q) and neoplasms (chapters II/III).

The diagnosis most frequently documented was slow fetal growth and fetal malnutrition (P05), followed by respiratory distress of the new-born (P22) and disorders related to short gestation and low birth weight, not elsewhere classified (P07).

For congenital anomalies (including all Q codes, D18.10, K40.9, P35.1, P83.5 and R01.1), 158 cases of major and minor anomalies were reported (table 4).

In 4.2% of the cases, at least one anomaly was reported (111/2672). The organ system most often affected was the

Table 2:
Health-related characteristics of mothers with exposure to at least one medication during a singleton pregnancy with available follow-up data.

Age (n = 2672)	**Number (n)**	**Percentage (%)**
<18 years	17	0.6
18–25 years	424	15.9
26–30 years	685	25.6
31–35 years	877	32.8
36–40 years	513	19.2
41–45 years	120	4.5
>45 years	12	0.4
Missing	24	0.9
Trimester at time of query		
1st trimester	1881	70.4
2nd trimester	457	17.1
3rd trimester	159	6.0
Missing	175	6.5
Past pregnancies (including current one)		
1 pregnancy	893	33.4
2 pregnancies	657	24.6
3 pregnancies	329	12.3
4 pregnancies	188	7.0
≥5 pregnancies	116	4.3
Missing	489	18.3
Past deliveries		
0 deliveries	1138	42.6
1 delivery	623	23.3
2 deliveries	294	11.0
3 deliveries	104	3.9
4 deliveries	14	0.5
≥ 5 deliveries	14	0.5
Missing	485	18.2
Risk factors		
Consumption of recreational or illicit substances	543	20.3
– Tobacco use	*331*	*12.4*
– Alcohol use	*112*	*4.2*
– Drug use	*100*	*3.7*
Psychosocial condition	97	3.6
Congenital condition in the family	27	1.0

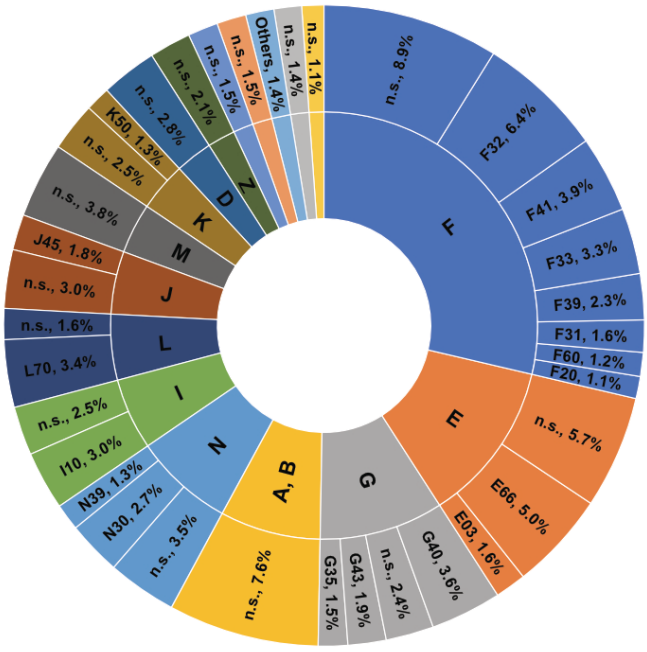
musculoskeletal system, followed by the circulatory system, congenital anomalies of the nervous system and chromosomal abnormalities. More specifically, the three most frequently documented diagnoses were congenital anomalies of cardiac septa (Q21), other congenital anomalies of the brain (Q04) and congenital anomalies of great arteries (Q25).

Discussion

Our work shows that a high number of queries were answered by the STIS over the last two decades. A large proportion of the queries concerned medications for the nervous system, of which psychoanaleptics (often selective serotonin reuptake inhibitors) and psycholeptics (often benzodiazepines) were the most frequent. This is likely to reflect not only the high prevalence of several mental disorders during pregnancy, such as depression and anxiety disorders, but also the complexity of the decisions behind their treatment.

In Switzerland, 17 % of women receive some form of mental health care during pregnancy and the first postpartum year [11]. Approximately 13% of the women participating in the recent survey in the Canton of Zurich reported acute mental disorders and 4% chronic mental disorders [6]. Representative data from France (pregnancies between 2010 and 2013) revealed depression as the most frequent maternal comorbidity in the year before and during pregnancy (20% prevalence) [12]. If left untreated, mental disorders during pregnancy can negatively influence pregnancy outcomes [13, 14]. Even though the widely used medication groups of selective serotonin reuptake inhibitors and benzodiazepines can be seen as appropriate during pregnancy when a pharmacological treatment is im-

Figure 5: Diagnoses of the mothers mentioned in the queries to the STIS. The ICD-10 classification was used. Note that only the cases of exposure to at least one medication during a singleton pregnancy and with available follow-up data were considered (n = 2233). The last five sectors (blue, orange, light blue, grey and yellow) are not labelled for readability reasons and correspond to the codes "H", "R", "Others", "V, W, X, Y" and "C". *The title of sector D is abbreviated and means "Neoplasms; Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism" in its full length.

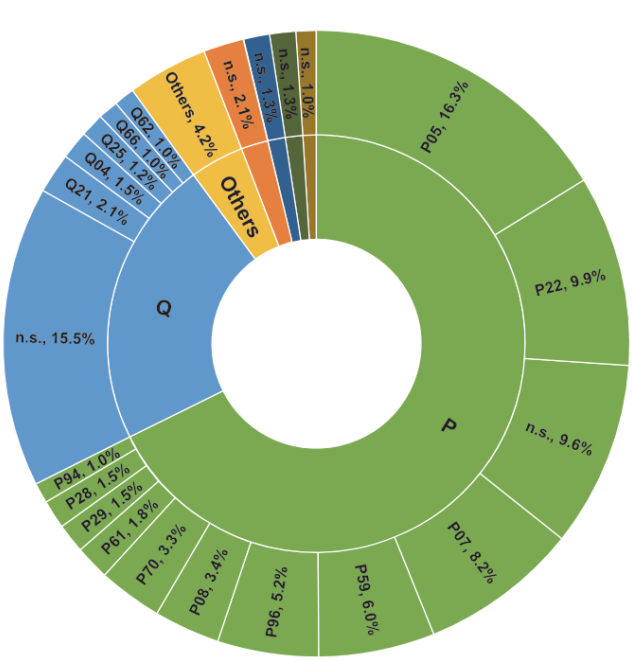


Codes	Description
F	***Mental and behavioural disorders***
F32	Depressive episode
F41	Other anxiety disorders
F33	Recurrent depressive disorder
F39	Unspecified mood [affective] disorder
F31	Bipolar affective disorder
F60	Specific personality disorders
F20	Schizophrenia
E	***Endocrine, nutritional and metabolic diseases***
E66	Obesity
E03	Other hypothyroidism
G	***Diseases of the nervous system***
G40	Epilepsy
G43	Migraine
G35	Multiple sclerosis
A, B	***Certain infectious and parasitic diseases***
N	***Diseases of the genitourinary system***
N30	Cystitis
N39	Other disorders of urinary system
I	***Diseases of the circulatory system***
I10	Essential (primary) hypertension
L	***Diseases of the skin and subcutaneous tissue***
L70	Acne
J	***Diseases of the respiratory system***
J45	Asthma
M	***Diseases of the musculoskeletal system and connective tissue***
K	***Diseases of the digestive system***
K50	Crohn disease [regional enteritis]
D*	***Neoplasms; Diseases of the blood and blood-forming organs***
Z	***Factors influencing health status and contact with health services***
H	***Diseases of the eye and ear***
R	***Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified***
V, W, X, Y	***External causes of morbidity and mortality***
C	***Malignant neoplasms***

Table 3:
ICD-10 categories for obstetric outcome after an exposure to at least one medication during a singleton pregnancy.

ICD-10 diagnoses (n = 393)		Number (n)	Percentage (%)
O24	Diabetes mellitus in pregnancy	65	16.5
O60	Preterm labour and delivery	48	12.2
O14	Pre-eclampsia	35	8.9
O16	Unspecified maternal hypertension	30	7.6
O41	Other disorders of amniotic fluid and membranes	29	7.4
O42	Premature rupture of membranes	26	6.6
O43	Placental disorders	19	4.8
O72	Postpartum haemorrhage	15	3.8
O21	Excessive vomiting in pregnancy	14	3.6
O40	Polyhydramnios	11	2.8
O26	Maternal care for other conditions predominantly related to pregnancy	11	2.8
O07	Failed attempted abortion	9	2.3
O23	Infections of genitourinary tract in pregnancy	9	2.3
O44	Placenta praevia	8	2.0
O99	Other maternal diseases classifiable elsewhere but complicating pregnancy, childbirth and the puerperium	8	2.0
O62	Abnormalities of forces of labour	5	1.3
O67	Labour and delivery complicated by intrapartum haemorrhage, not elsewhere classified	5	1.3
O68	Labour and delivery complicated by fetal stress [distress]	5	1.3
O73	Retained placenta and membranes, without haemorrhage	5	1.3
O20	Haemorrhage in early pregnancy	5	1.3
O45	Premature separation of placenta [abruptio placentae]	4	1.0
O13	Gestational [pregnancy-induced] hypertension	4	1.0
Others		23	5.9

Figure 6: Children's and obstetric outcomes documented in the follow-up of queries performed during singleton pregnancies upon exposure to medications. Children's as well as obstetric outcomes (n = 670) are classified according to ICD-10; codes indicating the pregnancy outcome were not considered. The orange, dark blue, dark green and brown sectors are not labelled, due to their small size and correspond to the codes "D", "I", "R" and "E". *without 96.4 **codes for malformations ***The title of sector D is abbreviated and should read "Neoplasms; Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism" in full length.



Codes	Description
P	***Certain conditions originating in the perinatal period***
P05	Slow fetal growth and fetal malnutrition
P22	Respiratory distress of newborn
P07	Disorders related to short gestation and low birth weight, not elsewhere classified
P59	Neonatal jaundice from other and unspecified causes
P96*	Other conditions originating in the perinatal period
P08	Disorders related to long gestation and high birth weight
P70	Transitory disorders of carbohydrate metabolism specific to fetus and newborn
P61	Other perinatal haematological disorders
P29	Cardiovascular disorders originating in the perinatal period
P28	Other respiratory conditions originating in the perinatal period
P94	Disorders of muscle tone of newborn
Q	***Congenital malformations, deformations and chromosomal abnormalities***
Q21**	Congenital malformations of cardiac septa
Q04**	Other congenital malformations of brain
Q25**	Congenital malformations of great arteries
Q66**	Congenital deformities of feet
Q62**	Congenital obstructive defects of renal pelvis and congenital malformations of ureter
D***	***Neoplasms; Diseases of the blood and blood-forming organs***
I	***Diseases of the circulatory system***
R	***Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified***
E	***Endocrine, nutritional and metabolic diseases***
n.s.	not specified

perative [15, 16], an individual risk assessment is required and some uncertainty is usually present. The latter is probably associated with inconsistent reports on possible associations of selective serotonin reuptake inhibitor use and various birth defects in the offspring (see e.g., [17, 18]), and with neonatal symptoms of the central nervous system after use of benzodiazepines in late pregnancy [19].

The uncertainty concerning the use of those medications for mental diseases explains why, in the present study, medication classes that are known to be commonly used tended to remain in the background. In a recent survey in canton Zürich [20], the most common medication classes used during pregnancy were painkillers, medications for acid-related disorders, and antibiotics (41.6%, 25.0% and 14.2%, respectively) [6]. This is in line with an analysis of the claims database from one of the main Swiss health insurance organisations [21], and comparable to what was observed, for example, in the USA, where the most commonly used medication classes were gastrointestinal/antiemetic agents, antibiotics, and painkillers [1]. In other, partly Swiss, studies, the most frequently recorded medications were analgesics, drugs for the gastrointestinal tract (e.g., antiemetics) and antibiotics [1, 6, 12]. Earlier work – based on prescription medications only – revealed that anti-infectives for systemic use and respiratory medications were the most frequently prescribed medications, at 41.3% and 28.0%, respectively [22]. In our study, queries concerning anti-infectives and medications for the alimentary tract and metabolism do not stand out as much as in these previous studies.

Our results suggest that physicians are particularly often concerned by (multiple) medication intake during pregnancy, which is understandable. They carry the main responsibility for the treatments that very often and due to lack of evidence are prescribed off-label [2] and, in the case of multiple treatments, for possible interactions. Multiple treatments were mentioned in approximately 50% of the queries (even after exclusion of vitamins, supplements, oral iron, chemicals and illicit or recreational drugs), and the polypharmacy rate – defined as intake of ≥5 medications – was 9.3%. Some overestimation of the risks of medication use during pregnancy might, however, play a role as well. A previous study conducted in collaboration with the STIS revealed that a majority of healthcare professionals in Switzerland had overestimated those risks [4]. Similarly, a Danish study showed that the safety risks of commonly used medications were accurately estimated by gynaecologists and obstetricians, whereas general practitioners overestimated the risks associated with two specific antidepressants [23]. Questions were frequently related to effects of treatments *per se* or treatment adjustments and submitted to the STIS during the first pregnancy trimester, when adjustments are usually due; only a few queries aimed at clarifying causality after an exposure. Despite STIS counselling services being available not only in French, but also in German and English, half of the queries came from the French-speaking canton of Vaud, where STIS is geographically located. This might be related to the STIS being associated with the CHUV, a well-known and highly respected hospital in this canton.

Follow-up information on the offspring revealed a malformation rate of 4.2%. When comparing this malformation rate with the malformation rate of 2.6% in the EUROCAT data [3], one must consider that in this database only major anomalies are included, and not minor and major anomalies as in our case. In general, comparison of malformation rates between different studies, time periods and countries is hampered by the complexity of the question and different malformation definitions (see e.g., [9, 24]). Often, the basal risk of malformation occurrence ranges between 1–3% [25–27] and up to 14% when birth defects among second trimester abortions are taken into account [28]. It should be added that in our work prevalence of malformations does not contain the bias of retrospectively reported anomalies, since we did not include retrospective data in the corresponding analysis (queries with a focus on causality assessment were excluded from part 2). We also found that the musculoskeletal system was the organ system most often affected, followed by the circulatory system. The most frequently documented congenital diagnoses were malformations of cardiac septa, other malformations of brain and malformations of major arteries. In other, but not all, populations, comparable patterns have been observed. In the EUROCAT population from 2000 to 2019, ventricular and atrial septal defects were also often seen, with a prevalence of 36.4 and 19.7 per 10,000 births,

Table 4:
ICD-10 categories for malformations observed after exposure to at least one medication during a singleton pregnancy.

ICD-10 diagnoses (n = 158)		Number (n)	Percentage (%)
Q65-Q79	Congenital malformations and deformations of the musculoskeletal system	40	25.3
Q20-Q28	Congenital malformations of the circulatory system	32	20.3
Q00-Q07	Congenital malformations of the nervous system	15	9.5
Q90-Q99	Chromosomal abnormalities, not elsewhere classified	15	9.5
Q60-Q64	Congenital malformations of the urinary system	13	8.2
Q10-Q18	Congenital malformations of eye, ear, face and neck	9	5.7
Q80-Q89	Other congenital malformations	9	5.7
Q38-Q45	Other congenital malformations of the digestive system	6	3.8
Q50-Q56	Congenital malformations of genital organs	5	3.2
Q35-Q37	Cleft lip and cleft palate	4	2.5
Q30-Q34	Congenital malformations of the respiratory system	2	1.3
K40.9	Inguinal hernia	2	1.3
P83.5	Congenital hydrocele	2	1.3
R01.1	Functional or unspecified cardiac murmur	2	1.3
D18.10	Lymphangioma: Hygroma colli cysticum	1	0.6
P35.1	Congenital cytomegalovirus infection	1	0.6

respectively [3]. In Taiwan, cardiovascular abnormalities were the most frequently seen birth defects, with ventricular and atrial septal defects amounting to 29.5 and 27.6 defects per 10,000 births [27], whereas in the Quebec birth cohort, musculoskeletal anomalies in 3.9% and malformations of the circulatory system in 2.3% of the cases were predominant [12].

Follow-up information showed further that elective and medical abortions amounted to 12.2% and spontaneous abortions to 6.6%, with live births at 80.4%. In pregnancy cohort studies performed in France and Canada, which both followed women from 1 year before pregnancy to at least 90 days post-partum, live births were documented in only 70.4% to 75.0% of cases, whereas the number of abortions rose to 29.2% (no differentiation between spontaneous and elective abortions) and 24.4% (5.8% spontaneous and 18.6% elective abortions) [12, 22]. The high frequency of short gestational age and prematurity is in line with the frequent obstetric diagnoses preterm labour and delivery, and premature rupture of membranes, and the values correspond to those of the general population. Prematurity affects approximately 7.1% of singleton pregnancies and low birth weight 5.2% (data from France, 2010–2013 [12]). The prematurity rate of new-borns in Switzerland was 6.7% in 2019; in the same year, 6.1% of the newborns showed a low birth weight (<2500 g) [29]. Prematurity is associated with a multitude of different risk factors and causes. In addition to multiple pregnancy, short cervical length, infections during pregnancy or tobacco and (illicit or recreational) drug consumption [30] can lead to preterm deliveries. Possible – direct or indirect – effects of specific medications are extremely difficult to investigate.

As a result of the consistency of the structured data acquisition and the collection of information on exposures during pregnancy by detailed medical history taken at the moment of first contact and at follow-up, the STIS database facilitates various research projects. Given the sample size of the STIS database and the variety of causes of birth defects [31], however, assessment of the safety and risk of specific medications is only possible through cooperation with the European Network of Teratology Information Services, ENTIS (see e.g. [32, 33]; more examples under [7]). Strengths of this STIS database characterisation with focus on consumption of medications during pregnancy are that it is based upon a large amount of data collected over a period of two decades and the availability of data on all medications used instead of only the drug specifically queried. Possible limitations of database analyses concern mainly the follow-up data. Due to the mostly short time period between birth and follow-up information, malformations that were only observed some time after birth are in most cases not documented in the database. Together with the lack of routine fetus examination after abortion, this may lead to misclassification regarding outcomes for children. Additional analyses of the queries about chemicals and paternal exposures during the same period of two decades are in preparation.

Conclusions

Healthcare professionals often have concerns on the treatment of pregnant women with medications and require professional counselling in this area. Psycholeptics and psychoanaleptics are the medications most often mentioned in the queries put to the STIS, showing that proper guidelines on their use during pregnancy are particularly urgent. Comedication deserves special attention as well. Better information on medication intake during pregnancy in general is a goal we should all strive for.

Data availability statement

All data analysed during the current study are available from Dr U. Winterfeld upon reasonable request.

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Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. APSW participates as an observer in the steering committee of the Swiss Academy for Perinatal Pharmacology. No other potential conflict of interest was disclosed.

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Appendix: Supplementary information

Identification of multiple pregnancies in the STIS-database

To be able to exclude multiple pregnancies in part 2, information had to be extracted from free text fields – mostly written in French, in a few cases English or German. These free text fields were therefore searched for the following terms: twin, triple, trichor (abbr.: trichorionic), triamni (abbr.: triamniotic), multiple, multipar (abbr.: multiparous), double, dual, second, second child, second embryo, second f(o)etus, other child, other embryo, other f(o)etus, Zwilling (Ger.: twin), Mehrling (Ger.: multiple), Drilling (Ger.: triplet), Vierling (Ger.: quadruplet), doppel (Ger.: double), zweit (Ger. abbr.: zweite/zweiter/zweites; second), zweite(s) kind, zweite(r) embryo, zweite(r) fetus (Ger.: second child, embryo or foetus), andere(s) kind, andere(r) embryo, andere(r) fetus (Ger.: other child, embryo or foetus), Föt (Ger. abbr.: foetus), Gemini (Lat.: twins), jumeaux (F.: male twins), jumelles (F.: female twins), gémellaire (F.: twin), deuxi (F. abbr.: deuxième; second), 2è/eme enfant, 2è/eme embryon, 2è/eme fœ/oetus (F.: second child, embryo or fetus), autre enfant, autre embryon, autre fœ/oetus (F.: other child, embryo or foetus), 1), 1., 2), 2., J1 (F. abbr.: jumeau 1; twin 1), J2 (F. abbr.: jumeau 2; twin 2).

Figure S1: Exposures to medications during singleton pregnancies with available follow-up documentation, depicted by anatomical main groups (n = 6583). *excluding sex hormones and insulins

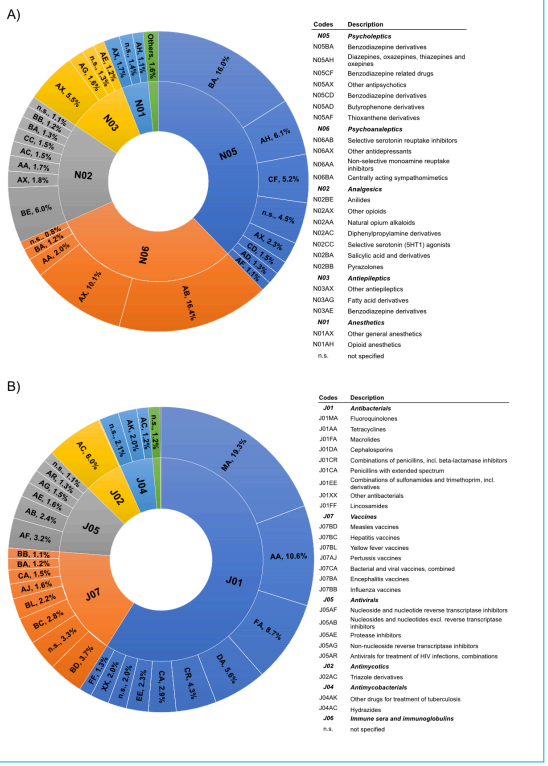

Figure S2: Therapeutic and chemical subgroups of medications for the nervous system (A, anatomical main group N; n = 2737) and anti-infectives for systemic use (B, anatomical main group J; n = 820) mentioned in the queries to the STIS. The light green sectors “Others” in figure 3A and “J06” in figure 3B are not labelled due to their small size. The subsector “n.s.” from the therapeutic subgroup “J02” and the sector “Others” in figure 3B are also not labelled due to their small size; they both amount to 0.1% respectively.

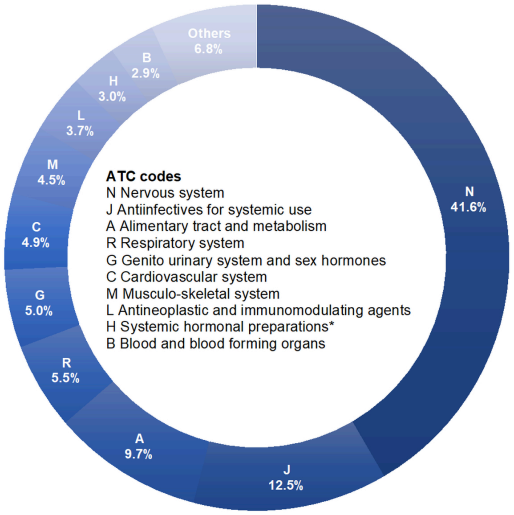

Table S1:
Pregnancy outcomes documented in the follow-up of queries during singleton pregnancies with exposures to medications.

Pregnancy outcome (n = 2672)	Number (n)	Percentage (%)
Live birth	2147	80.4
Elective/therapeutic abortion	325	12.2
Spontaneous abortion	177	6.6
Stillbirth	14	0.5
Others	9	0.3