European Journal of Obstetrics & Gynecology and Reproductive Biology 247 (2020) 42–48

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

Outcomes of drug exposition during pregnancy: Analysis from a teratology information service

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ARTICLE INFO

Article history:
Received 19 September 2019
Received in revised form 27 January 2020
Accepted 29 January 2020

Keywords:
Teratology
Pharmacoepidemiology
Pregnancy
Foetotoxicity
Malformation

ABSTRACT

Objective: We aimed to characterize drug exposures during pregnancy where the outcome was known that had benefited from counselling through our Teratology Information Service (TIS) between 1994–2016.
Study design: This observational study analysed data collected through the drug exposures during pregnancy counselling. Data was analysed descriptively.
Results: Data from a total of 1'374 pregnant women were collected. Mean age was of 32 years. These women were exposed to more than ten drugs in 1.4 % (N = 19) of cases, with a mean drug intake of two. Analysis of the drugs altogether (N = 3'129) showed that FDA Pregnancy Category C drugs represented 42.9 % (N = 1'342) of drugs and ATC code N (nervous system) represented 36.4 % (N = 1'138). The onset of drug exposure was during the first trimester of pregnancy in 95.1 % (N = 2'982) of patients. Regarding outcomes, the rate of induced abortion was 10.8 % (N = 151), of pregnancy complications was 11.2 % (N = 157) and of malformations was 4.5 % (N = 49).
Conclusion: Pregnant women counselled by our TIS take a mean of two drugs, ranging from one to 17. Drugs are from FDA Pregnancy Category C and ATC N drugs in most cases, 42.9 % and 36.4 % respectively. The rate of malformation of our cohort was of 4.5 %, close to the estimated spontaneous rate of malformation. This data gives a reassuring aspect of drug exposure in pregnancy but takes into account the outcome at birth only.

1 Introduction

Many pregnant women are exposed to drugs, either occasionally or for a prolonged period, due to acute or chronic illnesses. The percentage of women exposed during pregnancy varies according to age at the time of pregnancy, ethnicity, level of education, health insurance system and geographic region [1]. Half of all pregnancies are unplanned, making it common for women to be exposed involuntarily at the beginning of their pregnancy [2].

In a prospective cohort study of nulliparous women followed since the first trimester, 73.4 % of women took a drug during their pregnancy with 55.1 % taking at least one drug during the first trimester, the critical period for development [1]. Polypharmacy is defined as taking more than five drugs and the same study showed that this was the case for 13 % of pregnant women [1]. In another study, women received an average of 5.2 medications in the first trimester, 7.1 in the 2nd and 6.6 in the 3rd trimester [3].

In a 2011 meta-analysis, French women were those who were the most exposed to drugs during pregnancy with a mean of at least 10 different drugs which was far above estimates in all other countries included in the study (Netherlands, Germany, Norway, Denmark, Finland, Italy and the US) [4].

The most commonly prescribed drugs in the first trimester are those for the gastrointestinal system, followed by antibiotics and analgesics [1]. However, the most prevalent drug group among the consultations received by Embryotox (a centre for pharmacovigilance and counselling in embryonic toxicology located in Berlin) are the psychotropic drugs, representing 25 % of all drugs [2].

The knowledge of the risk associated with drug exposure during pregnancy has improved substantially since the thalidomide scandal 60 years ago. When a drug is marketed now, in vivo and in vitro studies estimate the risk associated with exposure during pregnancy. The International Council of Harmonization (ICH) provides recommendations (ICH S2 and S5) for the industry to

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https://doi.org/10.1016/j.ejogrb.2020.01.042
0301-2115/

highlight important factors for assessing the potential risk of a toxic effect in humans [5, 6]. However, clinical experience is still insufficient regarding the safety of drugs in pregnancy and often only epidemiological studies allow a risk assessment [2].

Adverse effects of drugs during pregnancy can be separated into two different categories, either teratogenic or foetotoxic. A teratogenic drug is defined as causing irreversible impairment to the newborn, affecting the organs during embryological development and thus causing birth defects. A foetotoxic drug is a drug that has a detrimental effect on foetal growth and organ function [7]. These effects can be due to the dose, the duration of exposure, the route of administration, the concomitant exposures, the period of exposure during pregnancy and potential genetic predispositions.

Since 2008, FDA does not recommend using the FDA risk categories anymore [8] and, in 2015, the FDA pregnancy risk classification system was replaced by the final Pregnancy and Lactation Rule [9]. From then on, FDA pregnancy risk categories also gradually disappeared from the Swiss Summary of Product Characteristics. The older FDA classification was as follows [8] :

- A: controlled studies in women do not show risk to the foetus in the first trimester
- B: animal reproduction studies do not show risk to the foetus but there are not controlled studies in pregnant women
- C: studies in animal show adverse effects on the foetus but there are not controlled studies in women
- D: there is positive evidence of human foetal risk, but benefits from use in pregnant women may be acceptable despite the risk
- X: studies in animal or human beings show foetal abnormalities and the risk of the use of the drug in pregnant women clearly outweighs any possible benefits

Knowledge of the potential adverse effects of drugs during pregnancy can help protect the mother and the baby. However, conversely, the overestimation of the associated risks may lead to withholding essential therapy, poor adherence, prescription of insufficiently studied drugs, invasive prenatal diagnostic tests or the recommendation to terminate a pregnancy [2]. A study compared pregnant women with an “average drug exposure” (teratogens and/or foetotoxic drugs excluded) and non-exposed or insignificantly exposed pregnant women and showed that the elective induced abortion rate (11 %) is higher in case of drug exposure while the rate of miscarriage and malformations were similar, with rates of 16 % and 3 % respectively [2]. The risk of major and minor malformations in the general population is estimated at 3–4 % and the aetiology of these is unknown in up to 70 % of cases [10]. Malformations due to drugs are thought to represent less than 2 % of this estimated risk [11].

Our Teratology Information Service (TIS) works by request for consultations by the physicians that follow pregnant woman exposed to a drug during pregnancy. These requests can come from the whole of Switzerland but most of them are from the French-speaking part.

Our TIS has been a dynamic and constantly improving centre over the last quarter of a century. During the last three years of the study, our TIS had a mean of 165 consultation requests per year. Follow-up for drug exposure during pregnancy is directly requested to the physician six weeks after the scheduled date of delivery. During the last three years of the study, follow-up was obtained in 88 % of cases.

The aim of our study was to describe the outcome of drug exposed pregnancies that we encountered among the consultations of our TIS, during more than 20 years of counselling. The TIS is part of the Division of Clinical Pharmacology and Toxicology of the Geneva University Hospital, Switzerland.

2 Methods

This study is a descriptive prospective cohort study conducted between 1994 and 2016. This study was approved by the research ethics committee of the canton of Geneva (No 2017-00625). The data were collected prospectively in the computerized database of clinical pharmacology consultations, the paper archives and the Excel files maintained since 1994 that collected the follow-up of the pregnancies.

2.1 Inclusion criteria

Consultation reports from the Division of Clinical Pharmacology and Toxicology of the University Hospital of Geneva between 1994 and 2016 that were on drug exposure during pregnancy and for which the outcome of the pregnancy was known.

2.2 Non-inclusion criteria

Consultation reports from the Division of Clinical Pharmacology and Toxicology of the University Hospital of Geneva between 1994 and 2016 that were on drug exposure during pregnancy but for which the outcome of the pregnancy was unknown or consultations requested before the pregnancy and resulting in no drug exposure during pregnancy.

2.3 Primary and secondary outcome

To characterise drug exposures during pregnancy among women included in our counselling service between 1994–2016. To provide a reasonable approximation of the malformation rate during pregnancy exposed to drugs and compare it to that found in the general population. To provide a reasonable approximation of the complication rate that occurred at delivery, such as preterm birth, intrauterine growth restriction (IUGR), respiratory distress syndrome, withdrawal and others (hypoglycaemia, icterus, oligoamnios..etc).

2.4 Statistical analysis

2.4.1 Data management

The data for the analysis were evaluated anonymously and consisted of:

- Maternal data : age, medical history
- Specific data concerning pregnancy : date of the last menstruation, estimated date of delivery
- Pregnancy outcome : delivery (premature or not), spontaneous abortion, elective induced abortion
- Newborn data: date of the birth, weight, Apgar score, clinical status (premature, birth defect, withdrawal symptoms . . .)
- Drug: International Nonproprietary Names (INN), ATC code, dose, route of administration, date of beginning and end of treatment

Drugs were classified according to the old FDA classification because it was the system used at the time when the drug exposures during pregnancy of our cohort happened. It also allows a classification of the risks of each drug. Moreover, the FDA risk categories are known to everyone and this makes it clearer to fully appraise the results.

2.4.2 Statistical strength and data analysis

This is a descriptive cohort study aimed at describing the outcome of drug exposure during pregnancy. There was no

hypothesis about the expected number of subjects. The analysis consisted of descriptive statistic data.

3 Results

A total of 1374 pregnant women were included in this study, the average age was 32 years old ranging from 14 to 48 years old. The most represented age group was the 30–34 age group (31.7 %). Half of the women were exposed to a single molecule (49.1 %, N = 674) with a maximal exposure of 17 molecules (N = 3) (Fig. 1).

The total of all drugs taken during these 1′374 pregnancies was of 3′129 as there was often more than one drug taken as mentioned above. Most counselling were for FDA class C or of unknown FDA pregnancy category with 42.9 % (N = 1′342) and 28.3 % (N = 886) respectively. FDA class X pregnancy category accounted for 4.9 % (N = 154) of the total of drugs (Fig. 2).

Most of the requests concerned drugs of the nervous system (ATC class N) and anti-infectious drugs (ATC class J) with 36.4 % (N = 1'138) and 17.9 % (N = 559) respectively of the total of all pregnancy medications (N = 3′129) (Fig. 3). Sedatives (e.g. alprazolam, zolpidem, bromazepam, midazolam . . .) and antidepressants/antipsychotics (e.g. clomipramine, amitriptyline, fluoxetine, citalopram, quetiapine . . .) accounted for 37.6 % (N = 428) and 30.6 % (N = 348) of drugs in the ATC class N, respectively (N = 1′141). Among the ATC class J (N = 559), antibiotics accounted for half of the requests (50.1 %, N = 280).

Drug therapy (N = 3′129) was almost always started in the first trimester of pregnancy (95.1 %, N = 2′982).

Outcomes were first analysed taking into account the total number of embryos/foetuses, that is, 1′374 pregnancies plus 22 twins of 22 twin pregnancies (N = 1′396).

On the whole cohort of embryos/foetuses (N = 1′396), there were 66.5 % normal neonates (N = 929) and 11.2 % neonates with complications (N = 157) for a total of 77.8 % live births (N = 1′086). Embryo/foetus/neonate deaths represented 14.6 % (N = 159) and could be further separated into 112 spontaneous abortions (8.0 %), 31 therapeutic terminations of pregnancy (2.2 %) and 16 other foetal deaths (1.1 %) (i.e. in-utero and neonatal deaths and ectopic pregnancies). Finally, 151 (10.8 %) pregnancies ended in an elective induced abortion.

Further analysis was done taking into account the number of live births.

Of all neonates (N = 1′086), 9.9 % (N = 107) were premature, this rate being higher in the 22 twin pregnancies with a rate of 68.2 % (N = 15) premature deliveries.

Of all neonates (N = 1′086), the rate of at least one complication was 14.5 % (N = 157) with 4.5 % (N = 49) being malformations (minor, major or chromosomal/genetic disorders). The different complications and the corresponding proportions are detailed in Table 1.

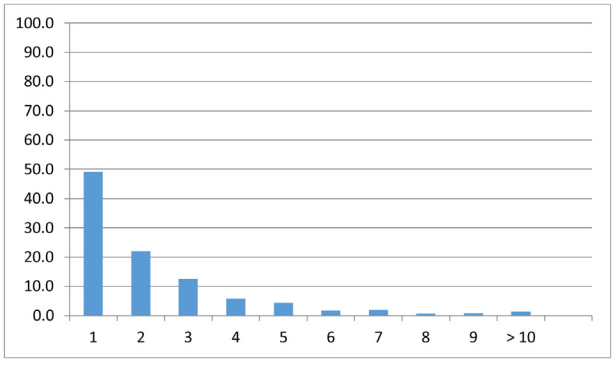

Fig. 1. Distribution of the number of drugs taken by each pregnant woman.

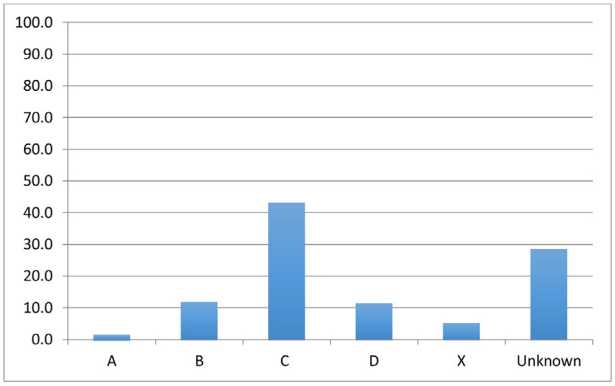

Fig. 2. Distribution of drugs according to the FDA classification.

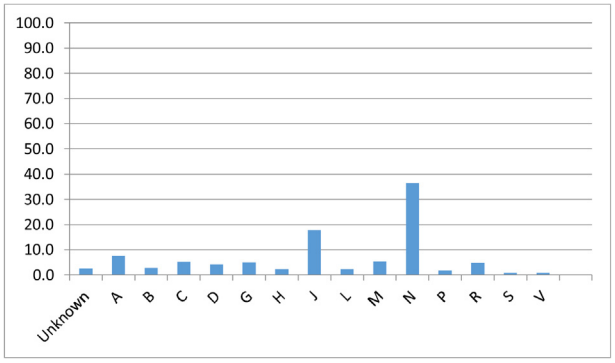

Fig. 3. Drug Distribution by ATC Class.

For intrauterine deaths and therapeutic terminations of pregnancy, one (trisomy 21) and four (trisomy 21, trisomy 18, spina bifida, major cardiac malformation) malformations were documented respectively. These malformations are not included in the calculation because we wanted to evaluate the impact of drug exposure during pregnancy on living malformations. All of the malformations encountered in the 49 neonates with malformations are detailed in Table 2.

The 49 malformations observed were after exposure to a total of 114 drugs, women often taking several drugs. Drugs from ATC class N (nervous system) represented 61 of these drugs and were present in 31 malformations. Drugs from ATC class A (alimentary tract and metabolism, e.g. antidiabetics, antiemetics) represented ten of these drugs and were present in five malformations. And finally, drugs from ATC class C (cardiovascular system) represented 10 of these drugs and were present in four malformations.

Among the 33 exposures to isotretinoin during pregnancy collected, there were twenty (60.6 %) therapeutic terminations of pregnancy, though none had a documented malformation, one ectopic pregnancy, two spontaneous abortions, one premature birth and nine normal outcomes (27.3 %).

Among the 15 exposures to valproate during pregnancy collected, there was one neonate with a malformation (absence of distal phalanx and syndactyly), four (26.7 %) elective induced abortions, one IUGR, one spontaneous abortion and eight (53.3 %) normal outcomes.

Among the 37 angiotensin-converting-enzyme (ACE) inhibitor and angiotensin II receptor blocker (ARB) exposures during pregnancy collected, there were twelve (31.6 %) premature births, fourteen (36.8 %) normal outcomes, one IUGR, five elective induced abortion), three spontaneous abortions, one renal insufficiency (resolving after discontinuation of treatment) and one malformation

Table 1
Details about complications.

Complication	Number (N)	Percentage	Expected rate
Neonates with malformation	49	4.5 %	3.4 %[1]
Intrauterine growth restriction	36	3.3 %	3–7 %[2–3]
Respiratory distress syndrome	21	1.9 %	Consistent variability between and among continent[4]. E.g. 17.9 per 100'000 person-years in Europe. Under-recognition incidence: 40–50 %[4]
Withdrawal	26	2.4 %	Variability between states and rural or urban infants[5]. 8.0/1000 hospital births in in 2014 in the US[6].
Other (e.g. hypoglycemia, icterus, hypernatremia, oligoamnios . . . etc.)	25	2.3 %	/
Total	**157**	**14.4%**	**/**

[1] https://www.entis-org.eu/.
[2] Vandenbosche RC, Kirchner JT. Intrauterine growth retardation. Am Fam Physician. 1998 Oct 15;58(6):1384-90, 1393-4.
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[5] Sanlorenzo LA, Stark AR, Patrick SW. Neonatal abstinence syndrome: an update. Curr Opin Pediatr. 2018 Apr;30(2):182-186.
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(clubfoot). Among the premature births, there were four births with complications (one respiratory distress syndrome, one withdrawal and two hypoglycemia and two cardiac malformations.

In most of these cases, other drugs were also taken concomitantly.

4 Discussion

It has been estimated that only 10 % of drugs marketed since 1980 have sufficient data on efficacy and safety during pregnancy, so the use of drugs during pregnancy is a decision based on the benefit/risk balance [12]. In addition to the risks associated with drug exposure, there are physiological changes during pregnancy that can lead to changes in the pharmacokinetic of the drugs [12]. For example, there is an increase in the amount of water in the body, of the volume of blood, of the volume of distribution and of the renal blood flow. Intestinal motility is impaired, liver enzyme values, albumin and plasma pH are reduced [12]. All of these can alter the foetal exposure by potentially increasing the plasmatic concentration of active drugs or metabolites and hence the teratogenic potential that can be dose-dependent.

Regarding the number of drugs taken, half of the women in our cohort were exposed to only one drug but several had multiple prescriptions, the number of drugs reaching 17 at the most. This is in line with other observations of drug exposure during pregnancy [1–4].

We chose to analyse our data using the old FDA classification because the requests at the moment of our study were tightly related to the FDA classification of the drug. Indeed, most reports of drug exposure during pregnancy of our cohort are for FDA class C or of an unknown class, so for drugs where either a risk exists in the animal but has not been tested in humans or where there is no data available. This reflects the concerns of doctors that ask for teratology counselling because information on these drugs is scarce or inexistent. Therefore, our analysis may underestimate the number of drugs from other classes taken by pregnant women, as practitioners did not ask counselling for drugs known to be harmless or conversely, drugs with known harms but required for treating the pregnant women.

In our cohort, regarding ATC class N (nervous system), antidepressant/antipsychotic were among the most commonly reported drugs taken during pregnancy. This can be explained in part by the fact that depression is common during pregnancy with a prevalence ranging from 7.4%–12.8 %, depending on the trimester [13]. There are three main categories of antidepressants (tricyclic, selective serotonin reuptake and serotonin/noradrenalin inhibitors) but the most extensively documented are SSRIs. Neonates exposed in-utero to SSRIs have an increased risk of morbidity and some small studies have demonstrated an increased risk for prematurity, admission to special neonatal care, poor neonatal adaptation including respiratory difficulties, low Apgar score, hypoglycaemia, feeding difficulties and cerebral excitation [14]. However, these effects are generally transient and SSRIs are considered to be the first choice of antidepressants when depression in pregnancy needs to be treated [14]. A systematic review and meta-analysis concluded that women who received SSRIs during pregnancy had a significantly higher risk of developing preterm birth compared with controls and this remained significant even when comparing depressed women only [15]. Moreover, an other systematic review and meta-analysis concluded that there is generally a small risk of congenital malformations and argued against a substantial teratogenic effect of SSRIs [16].

Concerning antipsychotics, data seems to be less abundant and prevents form assessing correctly the teratogenicity of these drugs [14]. Some studies show that second-generation drugs are not associated with congenital birth defects or neurodevelopmental problems [17]. A literature review conclude that antipsychotic drugs do not seem to increase the rate of major congenital anomalies or other foetal problems but studies did not fully consider the possible effects of maternal mental illness [18]. In fact, a study identified that women with severe mental illness had elevated rates of gestational hypertension, gestational diabetes mellitus, smoking and obesity in pregnancy, therefore studies that examine associated risks for severe mental disorders or their treatment should take into account these cofounding co-morbidities and exposures [19]. However, an epidemiologic study put in evidence an increased number of visits to the general practitioner for babies born to mothers on antipsychotics during pregnancy, but this may be biased due to the psychological status of the mothers [17]. The rate of birth defects when their mother has been exposed to antipsychotics is 4 % with clozapine and olanzapine, appearing to be riskier than other antipsychotics [14]. Nevertheless, evidence from a large study suggests that use of antipsychotics in the first trimester of pregnancy generally does not meaningfully increase the risk for congenital or cardiac malformations [20]. A systemic review found malformation rates of 3.5 % for olanzapine, 3.6 % for quetiapine and 5.1 % for risperidone, which does not increase the risk of malformation in a clinically meaningful way [21]. A literature review suggests that there is no increased risk of congenital malformations with second generation antipsychotics but apparent data on other pregnancy outcomes (preterm birth,

Table 2
Malformations encountered in our cohort and corresponding drug exposure.

Malformations	Drugs exposure during pregnancy	Described in the literature (yes/no) (broad PubMed search)
Cornelia de Lange syndrome (1 case)	- Patient 1 : amitryptiline	- No
Syndactyly (1 case)	- Patient 2 : budesonide	- No
Heart murmur (4 cases)	- Patient 3 : trovaflocaxin	- No
	- Patient 4 : norfloxacin	- No
	- Patient 5 : norfloxacin	- No
	- Patient 6 : lamotrigine, levothyroxine, salmeterol, salbutamol	- No for all drugs
Hypospadias (5 cases)	- Patient 7 : phentermine, flufenamic acid, diclofenac, tizanidine	- Yes for all drugs
	- Patient 8 : venlafaxine, lorazepam	- Yes, No
	- Patient 9 : mebeverine	- No
	- Patient 10 : venlafaxine, lorazepam	- Yes, No
	- Patient 11 : doxycycline	- No
Chiari malformation (1 case)	- Patient 12 : fluoxetine	- Yes
Clubfoot (3 cases)	- Patient 13 : hydrochlorothiazide, irbesartan, orlistat	- No for all drugs
	- Patient 14 : haloperidol, lorazepam	- No for all drugs
	- Patient 15 : olanzapine	- No
Ectrodactyly (1 case)	- Patient 16 : venlafaxine, metoclopramide, clotiapine, promazine, mefenamic acid	- No for all drugs
Pelvicalyceal dilatation (4 cases)	- Patient 17 : fosfomycin	- No
	- Patient 18 : minoxidil, betamethasone	- No for all drugs
	- Patient 19 : valacyclovir	- No
	- Patient 20 : valerian	- No
Tetralogy of Fallot (1 case)	- Patient 21 : clomipramine, mirtazapine, clorazepate, lorazepam	- No for all drugs
Syndactyly and ectrodactyly (1 case)	- Patient 22: valproate, cyclophosphamide, alprazolam, prednisone, omeprazole, salmeterol, levofloxacin	- No for all drugs
Pulmonary atresia (2 cases)	- Patient 23 : bendroflumethiazide	- No
	- Patient 24 : methoxypsoralen	- No
Cleft lip (1 case)	- Patient 25 : cabergoline, betamethasone	- Yes for all drugs
Hydrocephalus (1 case)	- Patient 26 : topiramate, venlafaxine	- No, Yes
Cleft palate (1 case)	- Patient 27 : amitryptiline	- No
Prader Willi syndrome (1 case)	- Patient 28 : sertraline, olanzapine, zolpidem, lorazepam	- No for all drugs
Frenulum of tongue (1 case)	- Patient 29 : citalopram	- No
Cardiac malformation (6 cases)	- Patient 30 : methylphenidate, methadone, oxazepam, venlafaxine, zolpidem	- Yes, No, No, Yes, No - Yes, No
	- Patient 31 : methylphenidate, methadone	- No for all drugs
	- Patient 32 : piroxicam, betamethasone	- No for all drugs
	- Patient 33 : furosemide, candesartan/hydrochlorothiazide	- No for all drugs
	- Patient 34 : emcitarabine, tenofovir, raltegravir	- No for all drugs
	- Patient 35 : zolpidem, dalteparin	
Hemangioma (1 case)	- Patient 36 : paroxetine, alprazolam, sertraline, lorazepam, pravastatin	- No for all drugs
Polydactyly (1 case)	- Patient 37 : citalopram, alprazolam, quetiapine, domperidone	- No for all drugs
Cystic fibrosis (1 case)	- Patient 38 : zopiclone, citalopram	- No for all drugs
Renal hypoplasia (1 case)	- Patient 39 : botulinum toxin	- No
Intellectual disability (1 case)	- Patient 40 : duloxetine	- Yes
Renal disability (2 cases)	- Patient 41 : citalopram	- No
	- Patient 42 : spironolactone, losartan, hydrochlorothiazide, atenolol, lisinopril, acetylsalicylic acid	- No for all drugs
Foramen ovale (2 cases)	- Patient 43 : sumatriptan	- No
	- Patient 44 : candesartan, metoprolol, lercanidipine, azathioprine, prednisone,	- No for all drugs
Flaps of periocular skin (1 case)	- Patient 45 : ciprofloxacin	- No
Arachnoid cyst (1 case)	- Patient 46 : balsalazide	- No
Diaphragmatic hernia (1 case)	- Patient 47 : lorazepam, buprenorphine	- No for all drugs
Sacro-coccygeal fossa (1 case)	- Patient 48 : sertraline, olanzapine, alprazolam, zolpidem, esomeprazole, sumatriptan, domperidone	- No for all drugs
Brachial plexus (1 case)	- Patient 49 : citalopram	- No

neonatal adaptation, miscarriage . . .) are insufficient to provide confident estimates [22]. Neonatal complications such as withdrawal symptoms, extra-pyramidal symptoms and respiratory problems may occur after the use of first and second generation antipsychotics in pregnant women [14]. The actual choice of drug for the individual pregnant patient must account for factors other than only safety data and take into account individual disease history, characteristics and treatment response, adverse reaction profile and patients preferences [22]. Moreover a systemic review and meta-analysis indicates that there is an increased risk of gestational diabetes mellitus with antipsychotic exposure in pregnant women, who may benefit from close pregnancy monitoring, lifestyle modifications, early testing for diabetes and targeting modifiable risk factors [23].

The other most frequent ATC class in our cohort were anti-infective drugs. Studies show that the prescription rate increases each trimester during pregnancy with the overall prescription of an antibiotic in 20.8 % of pregnancies [24]. In other studies, it has been estimated that one in four women will have an antibiotic prescription during pregnancy and this represents 80 % of prescriptions for a pregnant woman [12]. The most frequent infections that affect pregnant women are urinary tract infections, pyelonephritis, sexually transmitted infections and upper respiratory infections [12] and during pregnancy, untreated sexually transmitted diseases or urinary infections are associated with a higher risk of morbidity, such as low birth weight, premature birth, or spontaneous abortion [12]. However, exposure to antibiotics during pregnancy is associated also with short- or long-term

effects for children such as congenital anomalies, changes in intestinal flora, asthma, atopic dermatitis [12]. For example, the use of antibiotics during pregnancy could lead to childhood obesity, cerebral palsy or epilepsy, atopic dermatitis, or asthma, for example [12]. However, a recent retrospective study suggests that antibiotic use does not affect the risk of small or low gestational age birth weight or gestational diabetes mellitus in pregnant women [25]. Trimethoprim is associated with an increased risk of cardiovascular malformations or cleft lip and tetracyclines are associated with decreased bone growth and tooth discoloration [24]. However, a systematic review and meta-analysis suggests that the use of quinolone during the first trimester of pregnancy was not associated with an increased risk of birth defects, stillbirths, preterm birth or low birth weight [26]. Nevertheless, in a case-control study and after adjustment for potential cofounders, use of macrolides (excluding erythromycin), quinolones, tetracyclines, sulphonamides and metronidazole during early pregnancy was associated with an increased risk of spontaneous abortion [27].

Our study shows that concerns about drug exposures during pregnancy are more frequent in the first trimester. This can be explained by the fact that the pregnancy is often unplanned and unknown in the first weeks of pregnancy. A counselling on the risk of birth defects is requested as soon as the pregnancy is discovered. For women, treated for a chronic disease, counselling should ideally before pregnancy.

Prematurity is a major determinant of neonatal mortality/morbidity because it has long-term health consequences and premature infants are at increased risk of developing cerebral palsy, sensory and learning disabilities or respiratory problems [28]. Regarding neonatal deaths who are not due to congenital malformations, 28 % are due to preterm birth [28]. The WHO estimated the overall incidence of preterm birth at 9.6 % in 2005 in a systematic review, while the incidence is 7.4 % in Europe and North America [28]. This rate is similar to the rate found in our study suggesting that drug exposure does not increase the risk of prematurity.

The frequency of elective induced abortions is an important indicator of public health, with low rates generally associated with good access to high quality care and good use of contraceptive methods [29]. The elective induced abortion rate in Europe is 10.0 per 1000 women in 2008 [29]. In Switzerland, in the canton of Vaud, between 1990 and 1999, the rate of elective induced abortion was 8.9 per 1000 women with 63 % who declared that they had no contraception [30]. Lately, the Swiss Federal Statistical Office published data on the elective induced abortions in Switzerland and showed that the rate in the canton of Geneva in 2018 is of 12 per 1000 woman of reproductive age (15–44 years old) [31]. These rates are much lower than the one found in our study which is of 10.8 %. This can be explained by several hypotheses. First, most of the drugs reported are those of the central nervous system and may be taken therefore by patients with difficult socioeconomic conditions [30]. In addition, when our counselling service receives the request from the medical doctor, we know that sometimes the patient has already taken the decision to terminate her pregnancy because she considers that drug exposure is too risky or for other personal reasons, even before our teratology counselling. Drug exposure appears to be a risk factor for elective induced abortion, with studies citing a 16 % rate [2] even though drug exposure does not require such an intervention in most cases.

In contrast to this, the 4.6 % malformation rate in our cohort is in the normal range for the general population. Drug exposure does not appear to be a risk factor for malformation in Europe [10].

Spontaneous abortion affects 10–15 % of clinically attended pregnancies and has been linked to both the use of antidepressants and to depression [32]. The rate of spontaneous abortion in our study is lower than this, being of 8 % in this cohort highly exposed to antidepressants/antipsychotics

IUGR is found in 10 % of pregnancies and is associated with higher neonatal mortality/morbidity including prematurity, cerebral palsy, intrauterine death, neonatal death, obesity, hypertension or type II diabetes mellitus [33]. Incidence increases with maternal factors (weight, tobacco, socio-economic status, age, history, pre-eclampsia, anemia . . . etc), foetal factors (multiple gestation, infection, genetic syndrome) or adnexales factors [33]. In our study, IUGR appears in 2.6 % of pregnancies. Withdrawal syndromes and respiratory distress syndromes may be the consequence of the use of central nervous system drugs [33]. These appeared to be low in our study, being of approximately 2 %.

Our study describes the repercussion of drug exposure during pregnancy through our counselling service and has limitations. First, it was sometimes difficult to understand if the termination of pregnancy were voluntary or medically indicated. We also had scarce data on the use of tobacco, alcohol or prenatal vitamins or on the genetic history of parents. Very often, no information was available on the end date of the treatment. Analysis was also done for each drug ken separately and not taking into account polypharmacy. Finally, the outcome of pregnancy is known at the time of delivery only. Malformation, complications or developmental issues occurring later in the child's life were not available.

5 Conclusions

Pregnant women counselled by our information service take between one to seventeen different medications. Drugs are from FDA Pregnancy Category C in 42.9 % of the cases and from the ATC N drug category (nervous system) in 36.4 % of cases. Almost all exposures begin in the first trimester probably because women are not yet aware of their pregnancy. Despite these pregnancies that are all drug-exposed, the rate of malformation at birth of our cohort was of 4.5 %, close to the estimated spontaneous rate of malformation. The rate of the different complications is also close to the rates in the general population.

These data are reassuring about the effects of drug exposure in pregnancy but take into account only the outcome at birth and give no information on long-term developmental issues after drug exposure during pregnancy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Acknowledgments

None.

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