Frequency and type of medications and vaccines used during pregnancy

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Abstract

Providing safe pharmacotherapy for pregnant women is challenging. Nearly all pregnant women are prescribed or inadvertently receive medication during their pregnancy. We reviewed the scientific literature to identify the specific medications and vaccines that are most often used during pregnancy and described them by category and indication. Our interest was to update the research before the implementation of the recently released FDA labeling rule for pregnancy and lactation that eliminates the use of pregnancy categories in product labels. Our results confirm that most products taken during pregnancy are over-the-counter or in the former FDA pregnancy categories A or B. However, medications taken prior to pregnancy recognition (inadvertent exposures) and those prescribed for chronic illness such as allergies, depression, and pain are of concern. A better understanding of medication and vaccine utilization during pregnancy may help clinicians reduce inadvertent first trimester exposures and improve the safe and effective treatment of pregnant women.

Keywords

Pregnancy, drugs, vaccines, drug safety

Introduction

The management of patients with pre-existing diseases during pregnancy is challenging. There is no absolutely safe therapeutic approach, given the many variables that affect a drug's benefit: risk profile (e.g. embryonic/fetal age, duration and dose of exposure, genetic susceptibility, and drug administration, distribution, metabolism, and excretion, among others).^{1,2} For each one of these factors, the pharmacological approach may have its own specific risks to the mother, to the fetus, or to both, making it very difficult to prescribe the right medication, at the right dose, at the right time, for each patient.

It is also of critical importance to consider the potential impact of lack of treatment and disease exacerbation on pregnancy outcomes.³ Poorly controlled asthma, diabetes, cardiovascular, renal, and thyroid disease all have potentially adverse effects on a fetus.⁴ Depression during pregnancy can affect a woman's participation in prenatal care, make her more likely to use tobacco and alcohol during pregnancy, and may affect fetal growth and infant behavior.⁵

While over 90% of women use at least one prescription or over-the-counter (OTC) medication during pregnancy,⁶ 70% of the medications approved in the United States between 2000 and 2010 have no human pregnancy data and 98% have insufficient published data to determine teratogenic risk in humans.⁷

A 2006 UK-based study using the national General Practice Research Database found that 1 out of every 164 women was prescribed a US Food and Drug Administration (FDA)-designated pregnancy category X medication in early pregnancy⁸ (Table 1). An analysis of the National Ambulatory Medical Care Survey found that, from 1998 to 2000, 11.7 million US women of childbearing age were prescribed potentially teratogenic medications.¹⁰ Another study estimated that one of every six women in the US receives a prescription for a potentially teratogenic medication each year,¹¹ but only approximately 50% receive counseling about teratogenic risks and contraception.¹² Since half of all conceptions in the US are unplanned,¹³ many thousands of first trimester pregnancies may be exposed to medications of uncertain safety every year.

Public health initiatives that hope to offer better and safer options for pregnant women require an understanding of what medications and vaccines are most frequently used in pregnancy and the most common indications for such use.

Bonati et al.¹⁴ published the first review of the literature on this topic in 1990, examining 13 studies published from 1960 to 1988. Daw et al.¹⁵ updated the topic in 2011, identifying 17 additional relevant articles published between January 1989 and April 2010. We decided to

review and update the literature prior to the implementation of the recently released FDA rule, "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling" on 30 June 2015.¹⁶ This rule discontinues the use of pregnancy categories in product labels, replacing them with a narrative account of the human and animal pregnancy and breastmilk exposure data and risk assessment. While the rule will encourage the inclusion in the label of a more informative assessment of what is known about a product's safe use during pregnancy and lactation, it may also make it more difficult for prescribers to summarize drugs and vaccines by categories of teratogenic potential.

Materials and methods

To update the literature, we performed a review of published studies that addressed the frequency of medication and vaccine use during pregnancy. Articles published in peer-reviewed journals between 1 May 2010 to 18 January 2015 were identified in PubMed. The search strategy was broad, using the terms "medications pregnancy" (1886 articles), "vaccinations pregnancy" (987 articles), and "prescription drugs pregnancy" (173 articles).

The exclusion criteria for the initially selected papers were as follows:

We excluded articles:

- in languages other than English, French, Spanish, Italian, Portuguese, Swedish, and Norwegian;
- based on animal or in vitro studies;
- with data >20 years old;
- reporting only small datasets (<500 participants);
- without exposure trimester, duration, or frequency of drug use information;
- that were focused on one category of medication (i.e., antidepressants) or disease state (e.g. asthma).

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Table 1. FDA pregnancy categories.

Pregnancy Category	Characteristics
A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR. Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.
C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

Source: Federal register 1980; 44: 37434–37467.⁹

Many of the identified articles were rejected as not relevant by simple title and abstract review. The full texts of the remaining articles were retrieved and reviewed by one physician (DFW) to determine their final inclusion or exclusion. This process resulted in the four articles discussed below, three regarding medications and one concerning vaccines.

Results

Frequency of medication use by drug category

In 2014, Lupattelli et al.¹⁷ published results of a cross-sectional, web-based multinational survey of 9459 pregnant or recently delivered women between October 2011 and February 2012. Use of any medication for acute/short-term illnesses or chronic/long-term disorders during pregnancy constituted the outcome variables. Vitamins and mineral supplements were excluded. The authors found that 81.2% of the women reported the use of at least one medication. Almost 70% of the women reported the treatment of an acute or short-term illness and 17% reported treatments for chronic or long-term illnesses. The prevalence of total medication use during pregnancy varied considerably across several countries from 62.2% in Croatia to 95.1% in The Netherlands. Medications for the nervous system were the most commonly used drugs during pregnancy mainly due to analgesics, namely paracetamol (acetaminophen) and its combinations (Table 2).

Frequency of medication use by indication

Among the women participating in the Lupattelli et al.¹⁷ study, 98.7% reported an acute or short-term illness for which the indications were

headache, heartburn, pain, nausea, and urinary tract infections. A quarter of the women reported a chronic or long-term illness for which the leading indications were hypothyroidism, asthma, allergy, and depression (Table 3).

Australian authors found a different spectrum and frequency of indications for medication use during pregnancy.¹⁹ Using a questionnaire, Sawicki et al. assessed 819 women aged ≥ 18 years attending their 36th week antenatal visit. Among all participants, 39.3% reported a chronic health disorder, mostly asthma, blood-related disorders such as thrombosis, hemorrhage, and/or anemia, including pregnancy-related conditions, diabetes mellitus including gestational diabetes, vitamin and/or mineral deficiencies including pregnancy-related deficiencies, and hypertension including gestational hypertension. According to the authors, the higher percentage of chronic illnesses detected was likely because the participants did not clearly distinguish between pre-existing and pregnancy-induced conditions, so they were grouped together to avoid misclassification. Use of at least one prescribed medication for a chronic health condition was reported by 26.5% of the participants, most commonly drugs for anemia, medications for chronic airway conditions, vitamins and minerals, and drugs for diabetes.

Frequency of use of specific drugs in pregnancy

Thorpe et al.¹⁸ used two US multicenter, case-control studies—the Centers for Disease Control and Prevention's (CDC) National Birth Defects Prevention Study and the Slone Epidemiology Center Birth Defects Study—to obtain the prevalence of first trimester use of medications. Responses from 5381 mothers of infants without major birth defects were collected by computer-assisted telephone interviews: 1923 from the Sloane study and 3458 from the National Birth Defects Prevention Study. Medications that were exclusively used intravenously, locally (e.g. procaine) or topically (except those used intravaginally) were excluded from the analysis. Because products within a drug class can differ in exhibiting potentially harmful effects in pregnant women, medications reported by type and not by specific name (except oral contraceptives) were excluded as well. Due to variability in preparation, vitamins, minerals, herbal supplements, and vaccines were also excluded. The authors focused the analysis on the first trimester, the critical period of organogenesis.

Thorpe et al.'s¹⁸ study confirmed that medication use during pregnancy is widespread and their lists of conditions treated and medications used closely mirrors the list from other studies (Table 4). The authors concluded that although these are commonly used medications, few (2 out of 54 in their analysis) had robust data with which to evaluate the products' teratogenic risk potential. They concluded that, "For the vast majority of the commonly used medications, insufficient data exist to characterize fully the fetal risk when used during pregnancy, limiting opportunities for informed clinical decisions about the best management of maternal conditions."

Frequency of use of specific vaccines in pregnancy

The CDC in the US and Public Health England (PHE) in the UK currently recommend the following vaccines for:^{20,21}

All pregnant women:

- Influenza vaccination (inactivated vaccine) at any time during each pregnancy;
- Tdap (tetanus, diphtheria, acellular pertussis) vaccine (CDC), or dTaP/IPV (diphtheria, tetanus, acellular pertussis/inactivated polio) vaccine (PHE), during each pregnancy, ideally between 27 and 36 weeks' gestation (CDC) or 28 to 32 weeks (PHE) but up to 38 weeks if necessary.

Table 2. Prevalence of medication use among 9459 pregnant women in Western, Northern and Eastern Europe, North and South America and Australia.

Medication category	Percentage of women with medication use (total no. of pregnancies = 9459)			
	Anytime during pregnancy	1st trimester	2nd trimester	3rd trimester
Analgesics	56.0	37.7	44.1	35.8
Drugs for acid related disorders	34.3	21.5	27.8	27.6
Nasal preparations	16.4	11.4	13.0	11.1
Antibacterials for systemic use	14.0	8.9	11.2	9.6
Laxatives	10.3	7.4	8.8	7.8
Antihistamines for systemic use	9.6	8.2	7.8	6.1
Drugs for functional gastrointestinal disorders	6.9	5.7	5.4	4.0
Anti-inflammatory and antirheumatic products	5.4	4.0	4.2	3.6
Gynecological anti-infectives and antiseptics	4.3	2.7	3.6	2.7
Drugs for obstructive airway diseases	4.2	2.8	3.2	2.6
Thyroid therapy	4.2	2.6	2.9	2.1
Psychoanaleptics	2.9	2.2	2.3	1.9
Psycholeptics	2.2	1.8	1.7	1.5
Throat preparations	1.8	1.2	1.4	1.3
Cough and cold preparations	1.6	1.1	1.3	1.1
Unspecified medications of the respiratory system	1.5	1.1	1.2	1.0
Antiemetics and antinauseants	1.4	1.3	1.2	0.9
Antithrombotic agents	1.4	0.8	1.0	0.8
Immunostimulants	1.0	0.6	0.9	0.8
Corticosteroids for systemic use	1.0	0.7	0.8	0.7

Source: Adapted from Lupattelli et al.¹⁷

Pregnant women in the presence of another risk factor (e.g. on the basis of medical, occupational, lifestyle, or other indications) upon consultation with a health care provider:

- Pneumococcal polysaccharide vaccine (PPSV23);
- Hepatitis A vaccination, Hepatitis B vaccination;
- Meningococcal vaccination (olysaccharide or conjugate).

CDC and PHE recommend against the use of live attenuated virus vaccines during pregnancy including preparations for measles, mumps, rubella, (MMR) varicella (chickenpox), and varicella zoster (shingles).

Recommendations, however, do not reflect actual vaccine administration rates. Naleway et al.²² collected data from the vaccine safety datalink concerning pregnancies ending in 2002 through 2009. Vaccination rates per 1000 pregnancies were calculated by vaccine type. In total, 669,695 pregnancies were identified, during which 141,389 vaccinations were administered. The most commonly administered vaccine was trivalent inactivated influenza vaccine (Table 5).

As evidenced by the data, contraindicated live vaccines (MMR, varicella, rubella, and influenza live attenuated) have been administered to a considerable number of pregnant women. It is not known what proportion of pregnant women and/or their health care providers were aware of the pregnancies at the time of vaccination—many of these exposures may have been inadvertent.

Discussion

Medications

The treatment of medical conditions during pregnancy is often necessary, whether to improve the mothers' quality of life or to treat diseases that threaten their health, the babies' normal development, or the lives

of both. The rate at which pregnant women were prescribed or self-administered at least one medication in the studies we reviewed ranged from 62% to 95% by country, demonstrating that using an OTC or prescription medication during pregnancy is a common occurrence worldwide. In the largest study, we reviewed¹⁷ almost 99% of women reported an acute or short-term illness during pregnancy. Between 24 and 39% of pregnant women reported chronic or pregnancy-related conditions in the two studies that addressed that question.^{17,18}

Overall, the most frequently used medications in pregnancy, either prescription or OTC, were taken to treat common acute or short-term conditions that may be exacerbated by pregnancy—headaches and other aches and pain, heartburn/gastric reflux, constipation, nasal congestion/cold symptoms, nausea. The most common non-pregnancy-related chronic conditions for which medications were administered were allergy, asthma, thyroid conditions, and depression. Chronic conditions that might have been caused or exacerbated by pregnancy included anemia, diabetes, and hypertension.

Table 4 illustrates that the 52 medications used most commonly during pregnancy, either purposely or inadvertently, encompass the whole spectrum of FDA pregnancy categories. The labels of the 21 OTC compounds all advised pregnant women to consult a health care provider before using the product and three of these also cautioned against use in the third trimester.

The observed frequency of the use of medications during the first trimester of pregnancy (Tables 2 and 4) indicates that inadvertent exposures—those prior to the woman's knowledge of her pregnancy—are common and are a source of concern. It is, nonetheless, somewhat reassuring that the most utilized medications in the first trimester were OTC products and those in FDA categories A and B. The FDA evaluates potential fetal toxicity prior to approval of OTC status, and most of these products have historical pregnancy data that

Table 3. Prevalence of acute and chronic disorders and medication use.

Disorder and administered medications	Prevalence of disorder (%) and medication use (%) (n = 9459)
Acute/short-term disorders	
<i>Headache</i>	55.1
Paracetamol (including combinations)	29.3
Non-steroidal anti-inflammatory drugs	1.9
Acetyl salicylic acid (including combinations)	1.0
Opioid analgesics	0.8
Selective Serotonin (5-HT ₁ agonists)	0.4
<i>Heartburn</i>	66.2
Antacids (aluminium, salt combinations, antiflatulents)	15.4
Alginic acid complex/sucralfate/bismuth	10.7
Proton pump inhibitors	2.0
Antacid with calcium	1.9
H ₂ receptor antagonists	1.6
<i>Pain</i>	68.5
Paracetamol (including combinations)	11.4
Non-steroidal anti-inflammatory drugs	1.2
Opioid analgesics	1.1
<i>Nausea</i>	72.9
First generation antihistamines	5.6
Metoclopramide/domperidone/bromopride	3.3
Serotonin antagonists	0.6
<i>Urinary tract infection</i>	15.9
Unspecified penicillins	2.9
NOS antibacterials for systemic use	2.8
Penicillins with extended spectrum +/-beta-lactamase inhibitors	2.5
Nitrofurantoin cephalosporins	1.1
	0.9
Chronic/long-term disorders	
<i>Hypothyroidism</i>	4.1
Thyroid hormone/levothyroxine	3.7
<i>Asthma</i>	5.2
Inhalant selective beta-2 agonists	2.6
Adrenergics and other drugs for COPD	1.1
Inhalant glucocorticoids	1.0
Systemic selective beta-2 agonists	0.3
<i>Allergy</i>	8.8
Second generation antihistamines	2.0
Nasal corticosteroids	0.7
First generation antihistamines	0.8
<i>Depression</i>	3.7
SSRI ^a antidepressant	1.7
SNRI ^b /mianserine/trazodone/mirtazapine/bupropion	0.5
Anxiolytics, benzodiazepine	0.1
Antipsychotics quetiapine/olanzapine	0.1

Source: adapted from Lupattelli et al.¹⁸

COPD: Chronic obstructive pulmonary disease.

^aSSRI: Selective serotonin reuptake inhibitor.^bSNRI: Serotonin-noradrenaline reuptake inhibitor.

did not raise concern. Similarly, those medications in categories A and B have shown evidence of lack or low toxicity during gestation. In the studies reviewed here, category C and D medications were prescribed for allergy, asthma, depression/anxiety, or pain. Prescribing clinicians should be cognisant of the lack of data or the precautionary data that resulted in these categorizations. Potentially, alternative medications with better established safety profiles for use during pregnancy could be recommended for these pregnant women or women with childbearing potential.

The category X products that are listed in Table 4 were either hormonal contraceptives that failed to prevent the pregnancy or fertility drugs used to facilitate it. Counseling on the correct use of contraceptive methods and early recognition of pregnancy may help reduce the frequency of these exposures, but sometimes inadvertent exposures are unavoidable. The category X definition does not, by itself, equate to teratogenicity, rather it includes the qualification that the drug provides no clinical benefit during pregnancy. Studies have shown that inadvertent continuation of hormonal contraceptives during pregnancy does not increase the risk for major congenital anomalies.^{23,24} Some progestins are taken for infertility to help maintain the pregnancy in the first trimester. Close supervision by medical specialty staff is needed to help monitor the pregnancy and balance the benefits and risks of the continuation of hormonal products.

Vaccines

The most common vaccine received by pregnant women in the US was the inactivated influenza vaccine. Even taking into consideration the fact that some pregnancies may not have spanned the recommended vaccination months (Oct–Feb), the observed rate of vaccination (174 per 1000 pregnancies) is low for a highly recommended and efficacious intervention. Vaccination not only helps to prevent flu in the pregnant woman but can also protect her infant for up to six months after birth. Administering the flu vaccine to pregnant women was 92% effective in preventing hospitalization of infants for flu according to one study.²⁵ The low rate of vaccination may be a reflection of pregnant women's overestimation of drug risks during pregnancy,²⁶ and/or the fear of vaccine safety that is prevalent in some communities.²⁷ Public health efforts should be invested to improve the knowledge among health care providers and pregnant women that the flu vaccine is safe and effective.²⁸ Additionally, the finding that some pregnant women continue to receive vaccines that are contraindicated in pregnancy (MMR, varicella, rubella), should alert health care providers to always question women about the possibility of pregnancy and to perform a pregnancy test, when indicated, before administering these vaccines.

Limitations

It is challenging to formulate valid conclusions on observed inter-country differences regarding the use of specific medicines in pregnancy, especially in the presence of confounding factors such as the prevalence of indicated maternal conditions, the prescription status of medicines, and insurance coverage for drugs and vaccines. As Bonati et al.¹⁴ concluded almost 25 years ago, there is a need for a research protocol on drug use in pregnancy with standardized outcome variables. In its absence, there are significant inter-study differences in cohort definitions, gestational period construction, categorization of vitamins and minerals, inclusion of off-formulary medications, and risk classification, as well as in the nature and extent of reporting of methods and findings in published studies.

Our review included publications with data from several countries, under the assumption that pregnancies and approved medications are similar throughout the developed world. In this review, the use of prescription and OTC medications varied greatly (from 62% in Croatia to 95% in Iceland). Nevertheless, it is clear that prescription medication use in pregnancy is common. Because of the considerable

Table 4. Most common specific medications used in first trimester of pregnancy.

Substance name (examples of trade names)	Percentage of use (n = 5381)	FDA pregnancy category (from drug label)
Acetaminophen/paracetamol (e.g. Tylenol, Apacet)	55.8	OTC ^a
Ibuprofen (e.g. Advil, Alaxan, Brofen, Motrin, Paduden, Caldolor)	23.5	OTC (avoid in third trimester)
Docusate (e.g. Colace)	7.3	OTC
Pseudoephedrine (e.g. Sudafed)	6.4	OTC
Acetyl salicylic acid (e.g. Aspirin)	5.3	OTC (avoid in third trimester)
Progestins ^b (e.g. Depo-subQ provera, Med-Pro, Provera)	4.7	X
Naproxen (e.g. Aleve, Naprelan)	4.3	C (avoid in third trimester)
Diphenhydramine (e.g. Benadryl, ZzzQuil)	3.6	OTC
Loratadine (e.g. Claritin, Alavert)	3.4	C
Progesteron (e.g. Prometrium, Endometrin)	3.4	X
Albuterol (e.g. Ventolin, Proventil, ProAir HFA)	3.3	C
Estrogenic compounds ^c (e.g. Estinyl, Depo-Estradiol, Deladiol)	2.9	X
Dextromethorphan (e.g. Delsym, Bisolvon Dry)	2.9	OTC
Levothyroxin (e.g. Levothroid, Levoxyl, Synthroid, Unithroid)	2.8	A
Ondansetron (e.g. Zofran, Zofran ODT, Zuplenz)	2.7	B
Guaifenesin (e.g. Mucinex, Robitussin, Humibid, Tussin)	2.3	OTC
Azithromycin (e.g. Zithromax, Aruzilina, Zmax)	1.9	B
Clomiphene (e.g. Serophene, Clomid)	1.8	X
Cetirizine (e.g. Zyrtec, Alleroff)	1.8	OTC
Doxylamine (e.g. Doxytex, Unisom Sleep Tabs, Equate Sleep Aid)	1.8	OTC
Bismuth subsalicylate (e.g. Pepto-Bismol, Kaopectate, Bismatrol)	1.6	OTC
Sertraline (e.g. Zoloft, Lustral)	1.5	C
Fluticasone (e.g. Flovent)	1.5	C
Follitropin (e.g. Follistim, Gonal-F, Fostimon, Puregon, Follitrin)	1.4	X
Chlorpheniramine (e.g. Chlor-Trimeton, Chlorphen, Allergy Relief)	1.4	OTC
Fexofenadine (e.g. Allegra, Mucinex Allergy)	1.4	OTC
Hydrocodone (e.g. Zohydro ER, Vicodin)	1.3	C
Nitrofurantoin (e.g. Furadantin, Macrobid, Macroclantin, Furantoin)	1.3	B
Phenylephrine (e.g. Neo-Synephrine, Sudafe PE, Sudogest PE)	1.3	OTC
Fluoxetine (e.g. Prozac, Sarafem, Rapiflux)	1.0	C
Leuprolide (e.g. Lupron, Eligard)	0.9	X
Salmeterol (e.g. Serevent)	0.9	C
Ranitidine (e.g. Zantac, Deprizine)	0.9	OTC
Bupropion (e.g. Wellbutrin, Zyban)	0.9	C
Metformin (e.g. Fortamed, Glucophage, Glumetza, Riomet)	0.8	B
Oxycodone (e.g. OxiContin, Roxicodone, Oxecta, Oxyl R)	0.8	B
Insulin (e.g. Humalog, Humalog Mix, Levemir, Novolog) 0.8	0.8	B
Codeine (in mixed medications e.g. Cotablu, Phenflu CD, Colrex)	0.8	C
Metoclopramide (e.g. Reglan, Maxolon, Metozolf ODT)	0.7	B
Escitalopram (e.g. Lexapro)	0.7	C
Miconazole (e.g. Oravig)	0.7	OTC
Famotidine (e.g. Pepcid, Heartburn Relief)	0.7	OTC
Montelukast (e.g. Singulair)	0.6	B
Chorionic gonadotropine (e.g. Ovidrel, Novarel, Pregnyl)	0.6	X
Paroxetine (e.g. Paxil, Brisdelle, Paxeva)	0.6	D
Simethicone (e.g. Gas-X, Mylicon, Phazyme, Alka-Seltzer anti-gas)	0.6	OTC
Psyllium (e.g. Metamucil, Konsyl, Cilium)	0.6	OTC
Trimethoprim (e.g. Proloprim, Trimplex, Primisol)	0.5	C
Sulfamethoxazole (e.g. Gantanol; combi w. trimethoprim > Bactrim)	0.5	D

(continued)

Table 4. Continued

Substance name (examples of trade names)	Percentage of use (n = 5381)	FDA pregnancy category (from drug label)
Alprazolam (e.g. Xanax, Intensol, Niravam)	0.5	D
Omeprazole (e.g. Prilosec, Omep)	0.5	OTC
Oxymetazoline (e.g. Afrin, Afrin Sinus, Zicam Sinus Relief)	0.5	OTC

Source: adapted from Thorpe et al.¹⁸

OTC: over-the-counter; FDA: food and drug administration; NOS: nitric oxide synthase.

^aAll OTC product labels advised patients to consult physician prior to use.

^bIncluding desogestrel, etonogestrel (pill and implant), levonorgestrel, medroxyprogesterone, norelgestromin, norethindrone, norgestimate, not otherwise specified (NOS)-oral contraceptive (progestin only); excluding drospirenone and hydroxyprogesterone.

^cIncluding ethinyl estradiol, estradiol cypionate, and NOS estrogen.

Table 5. Most commonly administered vaccines in 669,695 pregnancies, 2002–2009.

Vaccine type	Total number of doses	Rate per 1000 pregnancies
Influenza (inactivated)	116,617	174.13
Tetanus-diphtheria-pertussis ^a	2695	6.34
Tetanus-diphtheria	4064	6.07
Human papillomavirus ^b	1821	5.40
Hepatitis B	2500	3.73
Hepatitis A	1570	2.34
Measles, mumps, rubella	799	1.19
Varicella	648	0.97
Meningococcal conjugate ^c	404	0.9
Typhoid (parenteral or oral)	450	0.67
Pneumococcal	378	0.56
Polio (inactivated)	275	0.41
Influenza (live, attenuated)	228	0.34
Meningococcal (polysaccharide)	121	0.18
Rubella	104	0.16
Diphtheria-tetanus-pertussis (DTap/DTP)	89	0.13
Yellow fever	67	0.1

Source: adapted from Naleway et al.²²

MMR: measles, mumps, rubella; HPV: human papillomavirus; Td/DT: tetanus-diphtheria; Tdap: Tetanus-diphtheria-pertussis.

^aTdap vaccine was first licensed for use in May 2005.

^bHPV vaccine was first licensed for use in June 2006.

^cMeningococcal conjugate vaccine was first licensed for use in January 2005.

heterogeneity in study methodology and exposure reporting, it was not possible to calculate pooled estimates of exposures and, thus, this review is limited to reporting the range of estimates among similar studies.

Information about vaccine administration during pregnancy focused on US data only because vaccination recommendations vary country-to-country and summary data were not identified in our search results.

Actual medication use was not possible to quantify. This review included research that relied on both medication distribution data and patient questionnaires to help arrive at reasonable estimates. Whether patients actually took the medication they were prescribed or recalled their medication intake accurately is unknown. OTC use was included in some studies and not in others, and inpatient drug utilization was not included at all.

Although this review uses FDA pregnancy classifications (A through X) to help assess pharmacotherapy risks, it should be noted that the classification system is being replaced by narrative descriptions with the upcoming implementation of the FDA labeling rule, "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling."¹⁶ This much-anticipated rule requires new or updated drug and vaccine labels to include a narrative summary of the risks of using the product during pregnancy and lactation and a discussion of the data supporting that summary. The labeling is also required to include relevant clinical information to help health care providers make prescribing decisions and counsel women about the use of medications during pregnancy and/or lactation. While a review of the narrative descriptions will require more time for review and evaluation by the health care provider, the main benefit is that the information provided will be more accurate and will enhance evidence-based clinical care. However, such information will need to rely upon data. The dearth of coordinated activity in the collection and study of medication exposures during pregnancy remains an obstacle to informed evidence-based clinical care.

Conclusion

A better understanding of medication and vaccine utilization during pregnancy can help prescribing clinicians reduce inadvertent first trimester exposures and improve the safe and effective treatment of women during pregnancy. In addition to refraining, if possible, from prescribing or recommending medications in the first trimester and only prescribing at any time when absolutely indicated, this review concludes with several practical reminders for health care providers.

1. Stay up-to-date on the potential for fetal harm among the medications you frequently prescribe to women of childbearing potential. Use medications with the most reassuring human data available. Counsel the patient appropriately.
2. Review the label prior to prescribing medications or administering vaccines whose potential fetal toxicities may be unfamiliar to you. The new pregnancy sections of the revised product labels following the implementation of the Pregnancy and Lactation Labeling Rule (PLLR) may contain additional data.
3. When prescribing medications or administering vaccines to women of childbearing potential, consider the potential risk for inadvertent pregnancy exposure. Perform a pregnancy test or counsel the patient regarding contraception, as appropriate.
4. Recommend the flu vaccine to your pregnant patients, reassuring them of its positive benefit:risk ratio and review the recommended adult vaccine schedule for postpartum administration.

Most pregnant women take one or more OTC or prescription medications during pregnancy for which there are little data regarding fetal

toxicity included in the prescribing information. The new FDA Pregnancy and Lactation Labeling Rule is one initiative to address this gap in knowledge. As clinicians, we should continue to be mindful of our role in the recommendation of drugs and biologics to women of childbearing potential.

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