Review Article

The Use of Medication in Pregnancy

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Summary

Background: Drug safety has the highest priority in the treatment of pregnant women, as any effect on fetal development will not be immediately evident, and the harm that ensues may have lifelong adverse consequences.

Methods: This review is based on pertinent publications retrieved by a selective literature search and on expert assessment on the basis of the current evidence.

Results: The teratogenic and fetotoxic drugs that are most important in their magnitude of effect and/or frequency of exposure are discussed, along with their characteristic effects. For each of the main indications for drug treatment during pregnancy, the current drugs of choice are stated, regardless of their approval status for use by pregnant women. Drugs are designated as "tolerable" in pregnancy if there is currently no reliable evidence of a human teratogenic effect but the state of the evidence is still inadequate for a conclusive determination. Such drugs can be given, in consideration of the risks and benefits, in case the drugs of choice are out of the question. Unplanned pregnancies arising in women who are taking "tolerable" drugs do not necessitate the immediate switch or discontinuation of the drug. On the other hand, drugs with known teratogenic or fetotoxic effects are designated as "contraindicated." For any pregnant woman exposed to such a drug, the risk must be assessed individually, and a risk management strategy must be determined.

Conclusion: For most indications for drug treatment in pregnant women, drugs are available with adequate clinical experience supporting drug safety. In all fields of medicine, drug safety information for pregnant women needs to be stated more precisely and in a manner more suitable for clinical application; moreover, the explanation to the patient must enable her to assess the risk realistically, but should not arouse undue anxiety. Drug safety in pregnancy demands the continuous collection of observational data, so that risks can be assessed as precisely as possible and false suspicions can be laid to rest, both for new drugs and for those that have already been in longstanding use. To this end, the Pharmacovigilance Institute (*Pharmakovigilanz- und Beratungszentrum*, PVZ) for Embryotoxicology critically assesses the current state of the evidence and carries out its own relevant observational studies.

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The use of medication in pregnancy is the norm—not the exception. According to a French study, drugs are prescribed to 90% of all pregnant women (1). However, there is still a sense of unease surrounding this topic, both among the healthcare providers and expectant mothers. It is not uncommon that uncertainties in the assessment of the fetal risks associated with the use of medication during pregnancy trigger irrational behavior, potentially resulting in withholding treatment, lack of compliance and overreactions, such as termination of a desired pregnancy after taking a supposedly "risky" medication. The "Contergan scandal" (the brand name of thalidomide in Germany), which occurred 60 years ago, is still in the mind of many people.

The safety of medication use in pregnancy always involves two individuals. The developing "co-treated" unborn child is at its most vulnerable stage of life. Unlike in children or adults, side effects affecting the embryo cannot be detected early enough to prevent potentially life-long damages. Thus, medication safety in pregnancy is of utmost importance.

For most indications, sufficiently proven medications are available. Detailed information about the tolerability and safety of medications in pregnancy or in persons desiring to have children can be found in textbooks (2), online databases (3, 4) and at specialized teratology information centers, such as the Pharmacovigilance Institute (*Pharmakovigilanz- und Beratungszentrum*, PVZ) for Embryotoxicology ("Embryotox", for short) in Berlin (5). By contrast, information provided in package inserts, in the German equivalent of the US Physicians' Desk Reference ("Rote Liste") and in summaries of product characteristics is usually not specific enough and at times misleading. These sources of information often highlight that the medication crosses the placenta and the lack of "controlled" trials; however, this is not helpful because almost all therapeutic agents cross the placenta to enter fetal circulation and because the evaluation of the safety of a medication is, for ethical reasons, primarily based on observational data. Both in the EU and in the United States, the provision of differentiated real-world information has been a requirement for the labeling of medicinal products with respect to pregnancy for some years now (6, 7), as has been the non-use of very superficial risk classification systems, such as the pregnancy categories Gr 1–11 used in Germany and the A, B, C, D, X system which has been in use in the United States for decades, despite being flawed by the same degree of imprecision. However, the shift from these

TABLE 1

The most important medications with proven teratogenic potential when used in the first trimester of pregnancy (according to [2–5, 27, 28])*1

Active ingredient	(Cardinal) signs and symptoms in the newborn/primarily affected organ systems
Unequivocal potent teratogens; monotherapy is associated with an up to 10-fold (30%) increased risk of gross structural malformations	
Retinoids, systemic (acitretin, etretinate, isotretinoin, tretinoin)	Ear, CNS, heart, skeleton
Thalidomide	Extremities, multiple malformations
Mycophenolate	Ear, palate
Valproic acid	Neural tube defect (lumbar spina bifida), heart, palate, urogenital system, extremities, dysmorphic facial features
Proven teratogens, monotherapy is associated with an up to 3-fold (10%) increased risk of gross structural malformations	
Androgens	Masculinization
Carbamazepine	Neural tube defect, heart, palate, urogenital system, extremities, dysmorphic facial features
Coumarin derivatives (phenprocoumon, warfarin)	Nose, extremities
Cyclophosphamide	Multiple malformations
Methotrexate*2	Multiple malformations
Misoprostol (for attempted induction of abortion)	Moebius sequence, extremities
Penicillamine	Cutis laxa
Phenobarbital/primidone (anticonvulsant treatment)	Heart, palate, urogenital system, extremities, dysmorphic facial features
Phenytoin	Heart, palate, urogenital system, extremities, dysmorphic facial features
Topiramate	Palate
Vitamin A (significantly more than 25 000 IU retinol/day)	As retinoids
Cytostatics (in general)*3	Multiple malformations
Discussed as so-called "weak teratogens" (risk 1:100 to 1:1000 exposed fetuses)	
Glucocorticoids (systemic)	Palate
Lithium	Heart (Ebstein anomaly, very rare)
Methimazole/thiamazole/carbimazole	Choanal atresia, tracheo-esophageal fistulas, aplasia cutis
Trimethoprim/Cotrimoxazol	Neural tube defect

*1 The medications listed here do not necessarily cause harm to the embryo. The risk of gross structural malformations associated with a monotherapy during the first trimester of pregnancy is rarely above 10%, with the exception of thalidomide, retinoids, mycophenolate, and valproic acid. Medications which are not included in this list must not be considered as proven safe.
*2 Risk associated with antirheumatic doses is lower
*3 Substance-specific evaluation required

classification systems to the now required detailed information about the evidence from studies available for each of the medications is far from being "universally" implemented – neither in the EU nor in North America.

In everyday clinical practice, off-label prescription to pregnant women can often not be avoided, because of the almost complete lack of drugs without pregnancy-related warnings. If there is no alternative to off-label use, that medication should be chosen from the pool of effective drugs which, according to current evidence, appears to be the safest for the unborn child (and the mother). Certainly, the pregnant patient has to be informed about the contradiction between product information and treatment decision—on the one hand, to ensure compliance and, on the other hand, to prevent unfounded assumptions of causality in case a coincidental congenital developmental disorder or a complication of pregnancy should occur.

No (effective) medication can offer 100% safety, as this would require to study infinitely large cohorts of exposed pregnant women. Therefore, any risk assessment of a medication only allows to state likelihoods and to compare this probability of risk with the probability of damage to the mother and child if the disease was left untreated.

When medication-related risks are discussed with a pregnant woman, the known background risks should be addressed. In approximately 3% of all fetuses/newborns, a so-called "major" malformation is observed (8). But only a small percentage (2–4%) of all congenital malformations can be definitely attributed to a chemical or physical cause, with maternal pharmacotherapy being one of those causative factors (9). Alcohol consumption is also included in this group and causes each year more fetal harm in Germany than any medication (10–12).

Methods

A selective search of the literature was performed, complemented by an expert opinion based on the current evidence.

Results

Rules for the use of medication in pregnancy

Care should be taken that any preexisting chronic condition is already well controlled and stable when planning a pregnancy in order to promote an uncomplicated pregnancy and prevent any potentially risky treatment escalations with additional medications during pregnancy.

More than 40% of pregnancies are not planned (13, 14). To prevent the use of unsafe medications in (early) pregnancy, all women of childbearing potential—making up nearly 20% of the German population—should be regarded as the target group of patients with pregnancy-compatible medication (15). In other words: Women with chronic conditions or recurrent episodes of illness should be treated with pregnancy-compatible drugs, even if no pregnancy is planned. Exceptions include the treatment of malignancies and treatment escalation to control an acute critical episode, for example in patients with systemic lupus erythematosus, inflammatory bowel disease, etc.

More than in other patients, it is necessary that specialists are responsible for the medication prescribed to pregnant women: This applies to the entire spectrum of conditions, from the treatment of acne to mental illness, to coagulation disorders, diabetes mellitus, thyroid disorders, and hypertension. Because pregnancy is usually only recognized during the highly sensitive period of embryogenesis, it is crucial that measures to protect the embryo against inadequate medication are already taken earlier. In all of their patients of childbearing potential, the treating gynecologist should have a multidisciplinary overview of medications being potentially inadequate in pregnancy.

Leaving a serious condition untreated may affect not only the pregnant woman, but also the development of her unborn child. Besides the selection of medications proven to be safe, the following general rule applies: "If the mother is well, her child is also well".

An effective treatment of a serious illness with a medication assumed to be incompatible with pregnancy (for example, a related warning in the summary of product characteristics) should not be abruptly discontinued at the time the patient is found to be pregnant, as this could jeopardize the success of the treatment and put the pregnancy at risk, potentially with adverse effects on the unborn child. Here, non-life-threatening conditions, such as retinoid therapy for skin diseases, are, of course, exemptions. Each case of unplanned pregnancy occurring under treatment with a supposedly incompatible medication always requires immediate clarification of the further procedure by the gynecologist and the specialist responsible for treating the disease.

In case of a life-threatening condition (e.g., oncology, cardiac emergency), optimization of the effectiveness of the maternal treatment is overriding the principle of avoiding a (supposed) teratogenic/fetotoxic risk. In these cases, optimized treatment of the mother can be vital to the survival of the unborn child. Here, treatment decisions are to be made on an individual basis, taking into account the diagnosis and the required treatment—apart from the fact that even with exposure to potent teratogens *(Table 1)* the malformation risk amounts to 30% at most; thus, the majority (more than 70%) of children with such prenatal exposure do not experience drug-induced harm (for example [16–18]).

Besides direct toxicity to the embryo or fetus, adverse drug reactions experienced by the pregnant woman can have an indirect effect on the unborn child; for example, the diabetic metabolic condition of the expectant mother associated with atypical antipsychotics may lead to fetal macrosomia (19).

In case drugs acting on the central nervous system, such as opioids, psychiatric medications and anticonvulsants, have been taken regularly until the end of pregnancy, the newborn may experience neonatal adaptation syndrome and present with symptoms such as irritability, sleep disturbances, high-pitched crying or sleepiness (20–22). Typically, these symptoms are mild and self-limiting, as observed, for example, with serotonin reuptake inhibitors (SSRIs). The use of benzodiazepines and lithium until birth may result in neonatal respiratory depression and longer lasting symptoms, through to floppy infant syndrome. In case of opioids, newborns experiencing severe withdrawal symptoms may require opioid replacement treatment.

In general, pregnant women regularly taking medication right up to childbirth, especially agents acting on the central nervous system, should plan to give birth in a perinatal center so that pediatric care is readily available should it be required. However, this must not be misunderstood as call to separate a

TABLE 2

The most important fetotoxic medications with adverse effects when used in the 2nd / 3rd trimester (according to [2–5, 27, 28])*

Active ingredient	(Cardinal) signs and symptoms in the newborn/primarily affected organ systems
Centrally acting drugs	
Benzodiazepines (long-term treatment or intrapartum)	Respiratory depression, adaptation syndrome, floppy infant syndrome
Lithium	Floppy infant syndrome, hypothyroidism
Opioids/narcotics (long-term treatment or intrapartum)	Withdrawal symptoms, respiratory depression
Psychiatric medications (general)	Adaptation syndrome, with SSRIs serotoninergic symptoms
Valproic acid	CNS functional disorder/potentially lower IQ
Others	
ACE inhibitors	Kidneys, oligohydramnios, anuria, joint contractures, hypoplasia of the skull
Aminoglycosides (systemic)	Inner ear and kidneys
Amiodarone	Hypothyroidism
Androgens	Masculinization
AT1-receptor blockers	Kidneys, oligohydramnios, anuria, joint contractures, hypoplasia of the skull
Azathioprine	Bone marrow depression
Coumarin derivatives (phenprocoumon, warfarin)	Intracerebral hemorrhage
Ergotamines (in contraction-ready uterus)	Fetal hypoxia
Radioiodine (in therapeutic dose)	Thyroid hypoplasia/aplasia
Tetracyclines (after 15 weeks' gestation)	Yellow discoloration of teeth
Antithyroid drugs	Hypothyroidism
Cytostatics (general)	Growth retardation, bone marrow depression

*Exposure does not necessarily cause the described signs and symptoms. Period of treatment and individual pharmacokinetics are decisive factors. Medications which are not included in this list must not be considered as proven safe.
ACE inhibitors, Angiotensin converting enzyme inhibitors; AT1, antagonist of angiotensin II type 1 receptors (synonym "sartans"); SSRIs, selective serotonin reuptake inhibitors

TABLE 3

Treatments of first choice by indications (according to [2, 4, 5, 24, 27, 28])

Indication	Treatment of first choice	Tolerable	Contra-indicated (evidence-based)	Comment
Acne	Antiseptics, antibiotics		Retinoids, esp. systemic	No consequences after local retinoid use
ADHD		Methylphenidate		Cautious indication
Allergy	Loratadine, cetirizine	Other H1 antagonists		
Anxiety disorder	Sertraline, citalopram	Venlafaxine rtd, other antidepressants*1		Neonatal adaptation syndrome possible
Antibiotic treatment	Penicillins, cephalosporins, erythromycin, azithromycin, clarithromycin, roxithromycin, spiramycin, fosfomycin	Cotrimoxazol, doxycycline up to 15 WG, ciprofloxacin, metronidazole, clindamycin, other antibiotics*1	Tetracyclines contraindicated from 16 WG	
Asthma	Inhaled short-acting beta2-agonists, e.g. salbutamol; ICS, e.g. budesonide; inhaled long-acting adrenergic agonists, e.g. formoterol (in combination with ICS)	Montelukast, theophylline rtd, tiotropium, omalizumab		Treatment according to treatment algorithm for non-pregnant patients
Bipolar disorder	Quetiapine, lamotrigine	Lithium, other established antipsychotics*1	No valproic acid prophylaxis	Continue lithium if well-controlled; neonatal adaptation syndrome possible, especially with lithium
Cholestasis	Ursodeoxycholic acid			
Compulsive symptoms	Sertraline, citalopram	Other established antidepressants*1		Neonatal adaptation syndrome possible
Condylomata acuminata	Cryotherapy, trichloroacetic acid, laser therapy, electrocautery			
Constipation	Bulking agents, lactulose, macrogol, bisacodyl		Anthrachinone, castor oil	
Cough treatment	Dextromethorphan, codeine (short-term)			
Depressive symptoms, agitated	Amitriptyline, mirtazapine	Other established antidepressants*1		Neonatal adaptation syndrome possible
Depressive symptoms, reduced motivation	Sertraline, citalopram	Other established antidepressants*1		Neonatal adaptation syndrome possible
Diabetes mellitus	Human insulin, metformin	Other established insulin analogs*1		Other oral antidiabetic agents are not recommended
Diuresis	Hydrochlorothiazide	Furosemide		
Enterobiasis	Pyrvinium embonate, mebendazole			
Epilepsy	Lamotrigine, levetiracetam	Oxcarbazepine, carbamazepine, clobazam	Valproic acid, topiramate	Valproic acid, topiramate only if better tolerated anticonvulsants were ineffective
Familial Mediterranean fever	Colchicine			Treatment required to stabilize pregnancy
Gastritis	Magaldrate, other antacids*1, famotidine, omeprazole			
Glaucoma	Timolol, dorzolamide, brinzolamide	Latanoprost		
Herpes	Aciclovir			
Hypertension (arterial)	Methyldopa, metoprolol	Bisoprolol, labetalol (not approved in Germany), nifedipine, amlodipine, urapidil, dihydralazine	AT1 receptor antagonist, ACE inhibitors after first trimester	If treatment is mandatory up to and including first trimester: prefer ACE inhibitors to AT1 receptor antagonist
Hyperthyroidism	Propylthiouracil; from second trimester: carbimazole, thiamazole			Preferably surgical treatment before pregnancy; residual risk of teratogenicity of antithyroid drugs cannot be excluded
Hypothyroidism	Thyroxine (T4)			No combination with T3
Inflammatory bowel disease	Mesalazine, olsalazine, sulfasalazine, azathioprine, 6-mercaptopurine, cyclosporine, prednisolone, local budesonide, potentially other corticosteroids	Infliximab, adalimumab, certolizumab		
Lice	Dimethicone			

Local anesthesia	All established agents, also combined with adrenaline			No bupivacaine in obstetrics (e.g. pudendal anesthesia)
Migraine	Sumatriptan, ibuprofen up to 28 WG, paracetamol	Zolmitriptan, rizatriptan, naproxen up to 28 WG	Ergotamine tartrate	Metoclopramide for associated nausea
Migraine prophylaxis	Metoprolol, amitriptyline		Valproic acid	
Multiple sclerosis	Interferon, glatiramer, prednisolone, azathioprine, immunoglobulins		Dimethyl fumarate, fingolimod	Individual treatment depending on disease course
Mycosis	Nystatin, clotrimazole, miconazole, amphotericin B	Fluconazole, itraconazole	Terbinafine	Avoid: Amorolfine, ciclopirox, naftifine, natamycin, tolciclate, tolnaftate; accidental use without consequences
Nausea	Doxylamine (with pyridoxine), dimenhydrinate, meclizine, metoclopramide	Ondansetron*3		Meclizine is currently not approved in Germany; import, if necessary
Pain	Ibuprofen up to 28 WG, paracetamol	Other NSAIDs/metamizole up to 28 WG, codeine, other opioids		Ibuprofen and other NSAIDs only up to 28 WG; Warning: Neonatal withdrawal symptoms after exposure to opioids; paracetamol controversial*2
Poisoning	In general, primary or secondary decontamination and administration of antidote as in non-pregnant patients			
Psychotic symptoms	Quetiapine, olanzapine, haloperidol, risperidone	Aripiprazole, other established antipsychotics*1		Neonatal adaptation syndrome possible
Reflux esophagitis	Omeprazole	Pantoprazole		
Restless legs	Cabergoline, levodopa			Cautious indication; available evidence sparse
Rheumatic diseases	Hydroxychloroquine, azathioprine, cyclosporine, prednisolone, established NSAIDs up to 28 WG	Adalimumab, infliximab, etanercept, certolizumab	Leflunomide, cyclophosphamide, methotrexate, mycophenolate	To date, no human teratogenicity proven for leflunomide; observe washout procedure
Scabies	Permethrin	Benzyl benzoate, crotamiton		
Secretolytic therapy	Acetylcysteine			
Sleep disorders, tension, restlessness	Diphenhydramine, amitriptyline, mirtazapine, promethazine, quetiapine	Zolpidem, zopiclone, lorazepam (all only short-term)		Warning: Neonatal withdrawal symptoms after exposure to benzodiazepines and Z-drugs
Thrombosis prophylaxis	Low-dose aspirin; fractionated, low-molecular-weight or unfractionated heparin	Clopidogrel	Vitamin K antagonists, such as phenprocoumon, warfarin	In case of vitamin K antagonists in early pregnancy, switch and fetal high-resolution ultrasound
Tuberculosis	Isoniazid, ethambutol, pyrazinamide, rifampicin			
Urinary tract infection	Penicillins, cephalosporins, fosfomycin	see Antibiotic treatment	see Antibiotic treatment	
Vaccinations	Diphtheria, tetanus, pertussis, influenza	Other inactivated vaccines if critically indicated	Live vaccines	No consequences after accidental administration of live vaccine in pregnancy

When starting a pregnant patient on a new treatment, preference should be given to treatments of first choice. If the treatment is not sufficiently effective or not tolerated, the medications classed as "tolerable" (the ones listed here represent only a selection of these medications) can be considered as alternative options. If a pregnancy is diagnosed while the patient is taking a "tolerable" medication, it is not necessary to abruptly discontinue this medication or switch to another medication. If a pregnancy is diagnosed while the patient is taking a contraindicated medication, this does not necessarily mean that the unborn child has been harmed. It is no reason to categorically question the pregnancy. Depending on the active ingredient and the timing, the likelihood of damage to the unborn child is in the range from "insignificant" to 30%. An individual risk assessment is required before a decision on the further management can be made. Neonatal adaptation syndrome may occur after exposure to any of the centrally acting agents (opioids, psychiatric medications, anticonvulsants) in the last weeks before delivery. Therefore, these patients should give birth in a perinatal center. However, "prophylactic" separation of a symptom-free child from the mother is by no means necessary. The table does not claim to be exhaustive in classifying medications into one of the three categories mentioned above. The optimal therapy in pregnancy must be decided on an individual basis by the physicians involved in the patient's care, taking into account the general treatment-guideline recommendations.

*1 This refers to other medications with a substantial body of evidence available on their use in pregnancy.

*2 In recent years, an association between paracetamol intake during pregnancy and abnormalities in the child, such as ADHD (29), delayed language development (30), cryptorchidism (31), and asthma (32, 33) have been observed in some studies. However, these findings should be interpreted with cautions given the methodological weaknesses of these studies, as their statistically significant results are based on comparatively small numbers of affected children. Recently, the successful use of paracetamol for closure of patent ductus arteriosus after birth (34, 35) has prompted discussion about the effect of paracetamol on the ductus arteriosus during the third trimester. Despite the global recommendation of paracetamol as an analgesic, no data from studies have yet become available, indicating a risk of cardiovascular adverse events in the fetus comparable to that of NSAIDs (36). Conversely, the absence of the effects postulated above cannot be proven with the available data. Ultimately, paracetamol remains the treatment of first choice and can be used throughout pregnancy in standard doses. However, it should not be taken over a prolonged period of time without critical evaluation.

*3 A Dear Doctor Letter on ondansetron issued because of a suspected low risk of cleft palate. However, this association has been critically challenged.

ADHD, attention deficit hyperactivity disorder; ICS, inhaled corticosteroids; NSAIDs, non-steroidal anti-inflammatory drugs; rtd, retard; WG, weeks' gestation

TABLE 4

**Risk characterization depends on clinical perspective.
Example: Paroxetine in pregnancy and heart defect—assuming a risk ratio (RR) of 1.5 for congenital heart defect after exposure to paroxetine in the first trimester (37, 38) and a prevalence (background risk) of almost 100/10 000 for congenital heart defects (8)**

Question	Answer
How many additional children will be born with a heart defect if 10 000 women take paroxetine during the first trimester?	50 children
What is the individual risk of a heart defect in the child if a pregnant woman took paroxetine in the first trimester?	1.5% instead of 1.0%
What is the probability of a causal association if a child has a heart defect after exposure in the first trimester?	1 : 2 (i.e. it is twice as likely that child's heart defect is unrelated to paroxetine exposure.)

TABLE 5

The 10 indications in pregnancy most frequently inquired about at the PVZ for Embryotoxicology*

Indication for treatment	%
Psychiatric disorders	23.9
Infections and infestations	17.2
Surgical and medical procedures	8.4
Nervous system disorders	7.6
Gastrointestinal disorders	6.2
Musculoskeletal and connective tissue disorders	4.6
Skin and subcutaneous tissue disorders	4.6
Respiratory, thoracic and mediastinal disorders	3.3
Pregnancy, puerperium and perinatal conditions	3.2
Injury, poisoning and procedural complications	2.7

* Analysis of the inquiries received at the PVZ for Embryotoxicology in 2018 by System Organ Classes (SOCs) according to MedDRA version 21.1.

symptom-free child after birth from its mother for "prophylactic" monitoring.

Occasionally, the question of the risk of long-term developmental disorders is raised, especially with regard to psychiatric medications. Although the extent and quality of the currently available data are still unsatisfactory, the experiences made so far indicate that the health of the mother, the social environment and the interaction with the child are at least as predictive of the later development of, for example, anxious or aggressive behavior as the prenatal exposure to medication (23–25).

To date, no active substance has been proven to be "paternally teratogenic" if taken by a fertile father at the time of conception. However, it should be noted that significantly fewer data on paternal teratogenicity are available compared to maternal data.

Table 1 summarizes the most important proven human teratogens which should not be used in pregnancy, especially not during the first trimester. *Table 2* lists the most important fetotoxins and their health effects associated with exposure in the second and third trimester of pregnancy. *Table 3* provides an overview of the treatments of first choice and "tolerable" second-line treatments, ordered by selected indications. The second-line treatments are usually less well studied and the evidence supporting their safety is less solid. It is critical to avoid prescribing medications which are contraindicated or clearly inadequate. However, it should be noted that intrauterine exposure to these drugs is by no means necessarily associated with damages to the unborn child. Whether it is harmed depends on the window of exposure, the dose and other, often unknown factors. Consequently, the accidental use of such medications in pregnancy should not always be regarded a high-risk situation, prompting abrupt discontinuation of the medication, unnecessary invasive diagnostic tests or even termination of pregnancy. Comprehensive high-resolution ultrasound assessment of the child ("fetal anomaly scan/organ ultrasound") is the most important diagnostic tool to evaluate the development of the fetus after critical exposure during the first trimester of pregnancy.

The question regarding the teratogenic risk of a medication must not be answered categorically with yes or no. Instead, current evidence-based information about the severity and likelihood of any malformations alleged to be caused by the medication should be provided. An overall rate of gross structural malformations above 10% is only found with very few teratogenic medications (*Table 1*). Comprehensive ultrasound assessment helps to obtain more precise information about any adverse effects caused by the medication. Furthermore, counseling about the medication-related risks should take the individual clinical situation (treatment recommendation, risk assessment of exposure that has already taken place during the pregnancy, causality evaluation in case of abnormalities/malformations) into account—see example in *Table 4*.

Embryotox and the safety of medication use in pregnancy

The Pharmacovigilance Institute (*Pharmakovigilanz- und Beratungszentrum*, PVZ) for Embryotoxicology (Embryotox) is part of the Charité Berlin and has been counselling the medical community and pregnant women since 1988. With financial support from the Senate Department for Health, Care and Equality of the Berlin Senate and the Federal Institute for Drugs and Medical Devices (BfArM, *Bundesinstitut für Arzneimittel und Medizinprodukte*) as well as industry-independent (research) project funding (by the DFG, Federal Association of the AOK, TK, KV Baden-Württemberg, among others), Embryotox has evolved to become the largest European reference center for medication safety in pregnancy. Some 14 000 consultations are performed each year,

covering the selection of suitable medications, consequences after (supposedly) unsuitable medication and differential diagnostic considerations with regard to prenatal developmental disorders after exposure to medication (also see *Table 5)*. In addition, the Embryotox online information portal at www.embryotox.de, covering the 430 most important medications, is accessed by, on average, 10 000 visitors daily. Via an online questionnaire system, individual counselling can also be initiated from this website. Information about medications in pregnancy in German is also offered by centers in Ulm (www.reprotox.de), Austria (Graz; www.embryotox.at) and Switzerland (Zurich; www.sappinfo.ch).

With the consultation at the PVZ for Embryotoxicology, a documentation of the course of the pregnancy is initiated with the patient's consent. The data obtained, including neonatal findings (recently in a pilot project up to age 2 years), are analyzed by the multidisciplinary Embryotox team on a case-by-case basis and the anonymized data are included in prospective cohort studies and case series. Abnormal pregnancy courses, some of which are received retrospectively by Embryotox as reports related to adverse drug reactions (so-called "ADR reports"), are passed on to the Federal Institute for Drugs and Medical Devices (BfArM) or the Paul Ehrlich Institute (PEI) after critical evaluation. These measures are intended to ensure continuous monitoring of medication safety in pregnancy. This strategy allows to generate or verify signals, quantify risks and rule out suspected associations. It does not only cover recently approved medications, but established medications as well.

The use of medication while breastfeeding

Although the information provided in package inserts may suggest otherwise: There are "breastfeeding-compatible" medications available for almost every indication. However, as with pregnancy, for information about these medications, special information resources, such as Embryotox or [2–5, 24, 26–28] have to be consulted. If the right medication is selected, there is no need for nursing breaks, expressing milk, let alone weaning. A single dose of hardly any medication poses a risk to the breastfed child—apart from a few exceptions, such as cytostatics and radionuclides. However, repeated intake or long-term medication may result, via the breast milk, in an accumulation of the medication in the infant and adverse reactions. This mainly applies to centrally acting drugs: opioids, psychiatric medications and anticonvulsants. The responsible pediatrician or midwife should be fully informed about the breastfeeding mother's medication intake. In general, the breastfed child should be monitored for the emergence of new signs and symptoms whenever the mother receives medication for several days. If adverse events are suspected, the concentration of the medication in the blood of the breastfed child should be determined and Embryotox should be contacted for further evaluation, if necessary. Young infants less than 2 months of age are more sensitive to any (long-term) medication of the mother; this applies in particular to premature infants. However, since preterm and ill infants benefit most from breast milk, maternal medication should not be taken as a reason to rush weaning in this sensitive population. Last but not least: After pregnancy may be before pregnancy. A woman can get pregnant while breastfeeding. Consequently, pregnancy-compatible medications should (also) be given preference while breastfeeding.

Key messages

- The differentiated characterization of the medication-related risk in pregnancy ensures compliance and prevents fears.
- Indiscriminate discontinuation of an effective medication can also pose a risk to the unborn child.
- Care should be taken that any preexisting chronic condition is already well controlled and stable when planning a pregnancy in order to prevent any potentially risky treatment escalations during pregnancy.
- All women of childbearing age should preferentially be treated with pregnancy-compatible medications.
- In all of their patients of childbearing potential, the treating gynecologists should have a multidisciplinary overview of medications being potentially inadequate in pregnancy.

Conclusion

Medications acceptable for use in pregnancy (and while breastfeeding) are available for almost all indications. Medication should be selected based on information in the qualified literature [2–5, 24, 26–28] or after consultation of relevant centers (for example Embryotox)—in case of chronic disease or recurrent symptoms requiring treatment, these medications should best be introduced before a pregnancy is established. Women of childbearing potential should primarily be treated with pregnancy-compatible medications. New or insufficiently studied medications are only acceptable if the treatments of first choice are not effective enough or not tolerated. It is mandatory not to use substances with proven developmental-toxic effect. Then again, the intake of a medication contraindicated in pregnancy does not necessarily represent a high-risk situation. The fact that such an exposure has occurred is by no means a valid reason to terminate the pregnancy. The counselling-associated documentation of the course of exposed pregnancies by Embryotox enables high-quality observational data to further clarify medication safety.

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Conflict of interest
The authors declare no conflict of interest.

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References

1. Berard A, Abbas-Chorfa F, Kassai B, et al.: The French Pregnancy Cohort: Medication use during pregnancy in the French population. PloS One 2019; 14: e0219095.
2. Schaefer C, Peters P, Miller RK: Drugs during pregnancy and lactation. 3rd. eds. New York: Elsevier/Academic Press; 2015.
3. Mother to baby: Medications & more during pregnancy & breastfeeding. Ask the experts. In: Fact Sheets. Organization of Teratology Information Specialists (OTIS), Brentwood, Tennessee. 2019. www.mothertobaby.org/fact-sheets-parent/. (last accessed on 1 September 2019).
4. Reprotox 2019. www.reprotox.org/. (last accessed on 1 September 2019).
5. Pharmakovigilanz- und Beratungszentrum für Embryonaltoxikologie. Berlin. 2019. www.embryotox.de. (last accessed on 1 September 2019).
6. Committee for Medicinal Products For Human Use (CHMP): Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling. London: European Medicines Agency; 2008. 1–18.
7. Food and Drug Administration, Department of Health and Human Services: Content and format of labeling for human prescription drug and biological products; requirements for pregnancy and lactation labeling. Final rule. 2014; 1–54.
8. European Platform on Rare Disease Registration: Prevalence per 10 000 births. All anomalies – 2011 to 2017 – All full registries – include genetic anomalies. www.eurocat-network.eu/accesspreva lencedata/prevalencetables. (last accessed on 1 September 2019).
9. Rösch C, Steinbicker V: Aetiology of congenital malformations-analysis of malformation registry data compared with the Kalter & Warkany-study (Abstract). Reprod Toxicol 2003; 17: 503–4.
10. Landgraf MN, Heinen F, et al.: S3-Leitlinie Diagnose der Fetalen Alkoholspektrumstörungen FASD. Langfassung. Gesellschaft für Neuropädiatrie (GNP); 2016. 1–221.
11. Lange S, Probst C, Gmel G, Rehm J, Burd L, Popova S: Global prevalence of fetal alcohol spectrum disorder among children and youth. A systematic review and meta-analysis. JAMA Pediatr 2017; 171: 948–56.
12. Landgraf MN, Nothacker M, Kopp IB, Heinen F: Clinical practice guideline: The diagnosis of fetal alcohol syndrome. Dtsch Arztebl Int 2013; 110: 703–10.
13. Finer LB, Zolna MR: Declines in unintended pregnancy in the United States, 2008–2011. N Engl J Med 2016; 374: 843–52.
14. Sedgh G, Singh S, Hussain R: Intended and unintended pregnancies worldwide in 2012 and recent trends. Stud Fam Plann 2014; 45: 301–14.
15. Statistisches Bundesamt: Bevölkerung und Erwerbstätigkeit. Bevölkerungsfortschreibung auf Grundlage des Zensus 2011, 2016: Statistisches Bundesamt (Destatis) 2019; 2019/01/31.
16. Coscia LA, Armenti DP, King RW, Sifontis NM, Constantinescu S, Moritz MJ: Update on the teratogenicity of maternal mycophenolate Mofetil. J Pediatr Genet 2015; 4: 42–55.
17. Henry D, Dormuth C, Winquist B, et al.: Occurrence of pregnancy and pregnancy outcomes during isotretinoin therapy. CMAJ 2016; 188: 723–30.
18. Tanoshima M, Kobayashi T, Tanoshima R, Beyene J, Koren G, Ito S: Risks of congenital malformations in offspring exposed to valproic acid in utero: a systematic review and cumulative meta-analysis. Clin Pharmacol Ther 2015; 98: 417–41.
19. Park Y, Hernandez-Diaz S, Bateman BT, et al.: Continuation of atypical antipsychotic medication during early pregnancy and the risk of gestational diabetes. Am J Psychiatry 2018; 175: 564–74.
20. Grigoriadis S, VonderPorten EH, Mamisashvili L, et al.: The effect of prenatal antidepressant exposure on neonatal adaptation: a systematic review and meta-analysis. J Clin Psychiatry 2013; 74: e309–e20.
21. Moses-Kolko EL, Bogen D, Perel J, et al.: Neonatal signs after late in utero exposure to serotonin reuptake inhibitors: literature review and implications for clinical applications. JAMA 2005; 293: 2372–83.
22. Newport DJ, Calamaras MR, DeVane CL, et al.: Atypical antipsychotic administration during late pregnancy: placental passage and obstetrical outcomes. Am J Psychiatry 2007; 164: 1214–20.
23. Nonnenmacher N, Noe D, Ehrenthal JC, Reck C: Postpartum bonding: the impact of maternal depression and adult attachment style. Arch Womens Ment Health 2016; 19: 927–35.
24. Rohde A, Dorsch V, Schaefer C: Psychopharmakotherapie in Schwangerschaft und Stillzeit. 4th edition Stuttgart: Thieme; 2016.
25. Erickson NL, Hancock GR, Oberlander TF, Brain U, Grunau RE, Gartstein MA: Prenatal SSRI antidepressant use and maternal internalizing symptoms during pregnancy and postpartum: exploring effects on infant temperament trajectories for boys and girls. J Affect Disord 2019; 258: 179–94.
26. LactMed: A toxnet database. drugs and lactation database. U.S. National Library of Medicine, Bethesda, MD. 2019. www.toxnet.nlm.nih.gov/newtoxnet/lactmed.htm (last accessed on 1 September 2019).
27. Schaefer C, Spielmann H, Vetter K, Weber-Schöndorfer C: Arzneimittel in Schwangerschaft und Stillzeit. 8th edition. Elsevier, Urban & Fischer; 2012.
28. Briggs GG, Freeman RK, Towers CV, Forinash AB: Drugs in pregnancy and lactation. 11th edition ed. Philadelphia: Wolters Kluwer; 2017.
29. Liew Z, Ritz B, Rebordosa C, Lee P-C, Olsen J: Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. JAMA Pediatr 2014; 168: 313–20.
30. Bornehag C-G, Reichenberg A, Hallerback MU, et al.: Prenatal exposure to acetaminophen and children's language development at 30 months. Eur Psychiatry 2018; 51: 98–103.
31. Snijder CA, Kortenkamp A, Steegers EAP, et al.: Intrauterine exposure to mild analgesics during pregnancy and the occurrence of cryptorchidism and hypospadia in the offspring: the Generation R Study. Human reproduction (Oxford, England) 2012; 27: 1191–201.
32. Henderson AJ, Shaheen SO: Acetaminophen and asthma. Paediatr Respir Rev 2013; 14: 9–16.
33. Shaheen SO, Lundholm C, Brew BK, Almqvist C: Prescribed analgesics in pregnancy and risk of childhood asthma. Eur Respir J 2019; 53. pii: 1801090.
34. El-Farrash RA, El Shimy MS, El-Sakka AS, Ahmed MG, Abdel-Moez DG: Efficacy and safety of oral paracetamol versus oral ibuprofen for closure of patent ductus arteriosus in preterm infants: a randomized controlled trial. J Matern Fetal Neonatal Med 2019; 32: 3647–54.
35. Ohlsson A, Shah PS: Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low birth weight infants. Cochrane Database Syst Rev 2018; 4: CD010061.
36. Dathe K, Frank J, Padberg S, et al.: Negligible risk of prenatal ductus arteriosus closure or fetal renal impairment after third trimester paracetamol use: evaluation of the German Embryotox cohort. BJOG 2019; [Epub ahead of print].
37. Wemakor A, Casson K, Garne E, et al.: Selective serotonin reuptake inhibitor antidepressant use in first trimester pregnancy and risk of specific congenital anomalies: a European register-based study. Eur J Epidemiol 2015; 30: 1187–98.
38. Wurst KE, Poole C, Ephross SA, Olshan AF: First trimester paroxetine use and the prevalence of congenital, specifically cardiac, defects: a meta-analysis of epidemiological studies. Birth Defects Res (Part A) 2010; 88: 159–70.

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