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Drugs to avoid preconceptionally

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Pharmacologic agents are unnecessary for normal pregnancy; however, some women plan pregnancy with medical conditions that require continuing or episodic treatment (e.g. asthma, epilepsy and hypertension). Moreover, during the reproductive years and during pregnancy, new medical problems may develop, and old ones can worsen (e.g. migraine headaches), to the extent of warranting pharmacologic therapy. In addition, many women consume prescribed and/or over-the-counter (OTC) medications during pregnancy^{1,2}. A comparison of therapeutic drug usage in pregnancy across Europe documented that 64% of women used at least one drug during their pregnancy³, while, in France, pregnant women were prescribed an average of five drugs during the first trimester². In the UK about one-third of women take pharmacological agents at least once in pregnancy, whereas only 6% take these agents in the first trimester⁴. Whereas it is plausible to collect data regarding the usage of medications in the preconception period, it would not be wrong to imagine that such usage is higher than the rates that have been documented in pregnancy.

Preconceptional counseling on the use of medications is of importance, as the consumption of medications is on the rise, new products are being marketed directly to the consumer and more prescription medications have been granted non-prescription status by the US Food and Drug Administration (FDA).

Though not widely practiced, unfortunately, drug regimens prescribed for chronic illnesses are best altered preconceptionally. In all probability, at least 10% of birth defects can be attributed to maternal drug exposure in pregnancy⁵.

COUNSELING FOR THE EXPECTANT MOTHER

The expectant mother should be counseled as to whether to continue or initiate a new medication in an open, supportive and informative manner. Most conditions that require medication involve drug exposures at low levels of relative and absolute risks. The goals of preconception medical management include: identifying patterns of medication and supplement use prior to conception; counseling women with chronic conditions about the potential impact of the condition and its various treatments on maternal and fetal health; establishing effective treatment for chronic conditions before conception; and counseling women to avoid the use of non-essential medications and OTC medications. Table 1 describes simple strategies for prescribing medication preconception and during pregnancy. Factors that affect the action(s) of the drug should be understood, including the FDA risk stratification of drug usage in pregnancy before prescribing (Table 2) and counseling an expectant mother.

Table 1 Useful strategies for prescribing medications in pregnancy and preconception

Avoid multiple medications if possible and choose those that are ‘safe’ (anticonvulsants, antihypertensives) and in the smallest dose possible

Determine what is the best method to monitor therapy (asthma: peak flow meters; hypertension: portable blood pressure monitors; diabetes: glucometers)

The healthiest mother is most likely to deliver the healthiest infant

Focus on the underlying disorder, not on the drug alone, to explain any additional risk to the fetus (hypertension and fetal growth restriction, seizures and childhood seizures, systemic lupus and fetal growth restriction)

Only a few drugs are clearly linked with specific birth defects (phenytoin, warfarin, alcohol, methotrexate, diethylstilbestrol, cis retinoic acid, valproic acid, carbamazepine)

Experience with first trimester exposure for any drug is often too limited in humans to be considered ‘safe’

Table 2 US FDA pregnancy category definitions

<i>Category</i>	<i>Description</i>
A	Controlled studies in women fail to show a risk to the fetus in the first trimester, and the possibility of fetal harm appears remote
B	Animal studies do not indicate a risk to the fetus and there are no controlled human studies, or animal studies do show an adverse effect on the fetus but well controlled studies in pregnant women have failed to demonstrate a risk to the fetus
C	Studies have shown the drug exerts animal teratogenic or embryocidal effects, but there are no controlled studies in women, or no studies are available in either animals or women
D	Positive evidence of human fetal risk exists, but benefits in certain (for example, life-threatening or serious diseases for which safer drugs cannot be used or are ineffective) may make use of the drug acceptable despite its risks
X	Studies in animals or humans have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience, or both, and the risk clearly outweighs any possible benefit

FACTORS AFFECTING THE EFFECT OF DRUGS DURING PRECONCEPTION

Safety information data

The safety and efficacy of drugs at a given dosage regimen is established by phase 3 clinical trials, involving numerous and typical representatives from the target patient population. Pregnant women and those who fall pregnant

during the trial are excluded from such studies. Thus, at a drug’s first marketing, except for products developed to treat conditions specific to pregnancy such as oxytocics and/or cervical ripening agents, human data on the proper dosage and frequency of administration during pregnancy seldom exist. All medications approved by the FDA must undergo animal studies to determine possible teratogenic effects. Doses (per body weight or surface

area) are often much higher than typically used to determine possible detrimental reproductive harm. Although such studies may be helpful, especially if findings indicate no additional risk, their results do not reliably predict the human response.

Pharmacokinetics of drugs in pregnancy

The physiological changes during pregnancy exert a marked impact on drug pharmacokinetics and hence established therapeutic ranges might be inappropriate. Pharmacokinetic changes during pregnancy include a higher volume of distribution, lower maximum plasma concentration, lower steady serum state concentration, shorter plasma half-life and higher clearance rate. As the placenta essentially acts as a lipid barrier between the maternal and fetal circulations and drugs cross it by passive diffusion, transfer of drugs to the fetus is unavoidable. In this regard, low molecular weight, lipid soluble and unionized drugs cross the placenta more readily than polar drugs.

Human teratogenesis

Teratogenesis is defined as structural or functional dysgenesis of the fetal organs. Typical manifestations include congenital malformations with varying severity, intrauterine growth restriction (IUGR), carcinogenesis and fetal death. Lack of understanding of the full and exact mechanisms of teratogenicity makes it difficult to predict, on pharmacological grounds, that a given drug will produce congenital malformations. Confirmation of pregnancy and accurate gestational dating are critical in determining susceptibilities, and 'all or none' effect (spontaneous abortion or not) is believed to result from exposure during the

ovum period (fertilization to implantation). In contrast, the embryonic period (implantation to 8th week of gestation) involves organogenesis and encompasses the most critical time with respect to structural malformations. Whereas specific harmful effects relate to the timing and duration of drug exposure during this relatively brief but critical time of development, information in humans is minimal or inconsistent regarding long-term effects, such as learning or behavior problems (functional teratogenesis) that may result from chronic prenatal exposure to given medications.

This chapter provides a quick reference guide for drug use in pregnancy. The drugs listed here are in groups according to how they appear in the WHO 11th Model List of Essential Drugs. A quick reference guide of drugs contraindicated in pregnancy (category X) is listed in Table 3.

ANESTHETICS

General anesthetics

Intravenous anesthetics induce anesthesia rapidly; common examples are thiopentone and propofol, though the latter has not been used during the first and second trimesters in humans. Reproduction studies in rats and rabbits at doses six times the recommended human induction dose revealed no evidence of impaired fertility or fetal harm.

Commonly used inhalation anesthetics include halothane and nitric oxide. Halothane can induce hepatotoxicity, and because of its property of relaxing the smooth uterine muscle it increases the risk of postpartum hemorrhage. The Collaborative Perinatal Project⁶ showed no embryonic or fetal effects associated with use of nitric oxide. Use during delivery, however, leads to neonatal depression

and fetal accumulation of nitric oxide, which increases over time. Therefore it is safer to keep the induction to delivery time as short as possible.

Neuromuscular blocking agents

These agents are used as adjuncts to anesthetics in order to provide muscle relaxation. Based on mechanism of action, they are divided into depolarizing and non-depolarizing agents. Succinylcholine is the only depolarizing agent commonly used. The Collaborative Perinatal Project⁶ recorded 50,282 mother-child pairs, 26 of whom had first trimester exposure to succinylcholine. No congenital malformations were observed in any of the newborns.

ANALGESICS, ANTIPYRETICS, NON-STEROIDAL ANTI-INFLAMMATORY DRUGS, DRUGS USED TO TREAT GOUT AND DISEASE-MODIFYING AGENTS USED IN RHEUMATIC DISORDERS

Non-opioid analgesics, antipyretics and non-steroidal anti-inflammatory drugs

Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) do not produce structural defects. Salicylates (in analgesic doses) and NSAIDs may increase the risk of neonatal hemorrhage by inhibition of platelet function. NSAIDs may also lead to oligohydramnios by their effect on the fetal kidney. The use of NSAIDs in the last trimester causes premature closure of the ductus arteriosus leading

Table 3 Examples of contraindicated drugs and their known adverse effects on the developing human fetus

<i>Drugs</i>	<i>First-trimester fetal effects</i>	<i>Second- and third-trimester fetal effects</i>
Quinolones	Toxic to developing cartilage	
NSAIDs		Cardiac, gastroschisis, miscarriage, premature ductal closure
Methotrexate	Miscarriage, cranial anomalies	IUGR
Immunosuppressants	Embryopathy	
Doxycycline		Effect on bone growth
I-131	Fetal thyroid development, CNS development	
Chemotherapeutics	Abortion, anomalies	Hypoplastic gonads, IUGR
Antabuse	Congenital malformations	
ACE inhibitors	Cardiac/CNS malformations	Oligohydramnios, IUGR, renal failure
Retin-A derivatives	CNS, cardiac, facial anomalies	Stillbirth, mental retardation
Streptomycin	Ototoxicity	None known
Tetracycline	None known	Staining of teeth
Thalidomide	Limb reduction (gastrointestinal/ cardiac/renal defects)	
Warfarin	Skeletal defects CNS defects	Microhemorrhages

IUGR, intrauterine growth retardation; ACE, angiotensin converting enzyme; CNS, central nervous system

to neonatal primary hypertension. Both premature closure of the ductus and the oligohydramnios are reversible. If used during pregnancy, NSAIDs should be discontinued at least 6–8 weeks before delivery.

Opioid analgesics

In a surveillance study of Michigan Medicaid recipients, 375 (4.9%) major birth defects were noted (325 expected)⁷. Specific data were available for six defect categories, including (observed/expected) 74/76 cardiovascular defects, 14/13 oral clefts, 4/4 spina bifida, 25/22 polydactyly, 15/13 limb reduction defects and 14/18 hypospadias. Only with the total number of defects is there a suggestion of an association between codeine and congenital defects, but other reasons, including maternal disease, concurrent drug use and chance may be involved. In an investigation of 1427 malformed newborns compared with 3001 controls, first trimester use of narcotic analgesics (codeine most commonly) is associated with inguinal hernias, cardiac and circulatory defects, cleft lip and palate, dislocated hip and other musculoskeletal defects. These data serve as a possible warning that indiscriminate use of codeine may present a risk to the fetus. Use of codeine during labor produces neonatal respiratory depression to the same degree as other narcotic analgesics. Neonatal codeine withdrawal has also been reported⁸.

Drugs used to treat gout

Colchicine is used to treat the pain of acute gouty arthritis attacks and as prophylaxis for recurrent gout attacks. It is also used in familial Mediterranean fever, Behcet's disease and amyloidosis. It is embryocidal in mice and rabbits, but the risk of teratogenesis in humans is unknown. It is possible that colchicine given around the time of conception may

result in an increased frequency of trisomy 21 in the offspring by causing chromosomal nondysjunction. If used around conception, fetal karyotyping is recommended. In a couple planning a pregnancy colchicine ingestion by either parent should be discontinued 3 months before conception⁷.

Disease-modifying agents of rheumatic disorders

Sulfasalazine

Sulfasalazine and its metabolite, sulfapyridine, readily cross the placenta to the fetal circulation. No increase in human congenital defects or newborn toxicity has been observed from its use in pregnancy. Milk concentrations are roughly 40–60% of maternal serum levels. Bloody diarrhea in an exclusively breastfed infant was attributed to the mother's sulfasalazine therapy (3g/day). Cautious use of sulfasalazine is recommended in nursing women because of significant adverse effects in some nursing infants.

Cyclophosphamide

Various abnormalities ranging from karyotyping abnormalities to multiple structural anomalies have been described with the use of cyclophosphamide in the first trimester. Use of cyclophosphamide in the second and third trimesters does not place the fetus at risk for congenital defects. Except in a few individual cases, long-term studies of growth and mental development in offspring exposed to cyclophosphamide during the second trimester, the period of neuroblast multiplication, have not been conducted. Cyclophosphamide is contraindicated during breastfeeding because of a reported case of neutropenia and because of the potential adverse effects of immune

suppression, fetal growth retardation and carcinogenesis.

ANTICONVULSANTS/ANTIEPILEPTICS

Phenytoin, primidone, phenobarbitone, carbamazepine and sodium valproate all cross the placenta and are teratogenic. The major abnormalities produced by anticonvulsants are neural tube, orofacial and congenital heart defects. Neural tube defects are mainly caused by sodium valproate (1–2%) and carbamazepine (0.5–1%). Orofacial defects are mainly from phenytoin, which also produces the fetal hydantoin syndrome. The syndrome includes prenatal and postnatal growth restriction, motor or mental deficiency, short nose with broad nasal bridge, microcephaly, hypertelorism, strabismus, epicanthus, wide fontanelles, low-set or abnormally formed ears, limb deformities, nail and distal phalange hypoplasia, hypospadias, hernia, webbed neck, low hairline, impaired neurodevelopment and low performance scores on tests of intelligence. Phenytoin and sodium valproate also produce heart defects. Primidone produces abnormalities similar to those produced by phenytoin.

The risk for any single drug is about 6–7% (i.e. two to three times the background level). The risk increases with multiple drugs. Patients on two or more anticonvulsants carry a risk of 15%, and for those taking a combination of valproate, carbamazepine and phenytoin the risk is as high as 50%. The risk of neural tube defects may be decreased with consumption of preconceptional and first trimester folic acid at a dose of 5 mg/day, i.e., more than 10 times the recommended dose of 400 µg/day for normal pregnant woman. Because the newer anticonvulsant drugs such as vigabatrin, lamotrigine, topiramate and gabapentin are often prescribed in combination with other anticonvulsants, it is difficult to ascertain the teratogenic risk of these agents in isolation. Monotherapy should be used wherever

possible, and special care should be taken to keep doses as low as possible and compatible with seizure prophylaxis. To lower the risk of hemorrhagic disease of the newborn, vitamin K (10–20 mg orally) should be prescribed for all epileptic women on enzyme-inducing drugs in the last 4 weeks of pregnancy.

The traditional anticonvulsants, such as phenytoin, carbamazepine and valproic acid, are considered safe for use during breastfeeding; however, observation for adverse effects such as drowsiness is recommended for women receiving high doses. The use of phenobarbital with breastfeeding is controversial because of its slow elimination by the infant. Data are sparse regarding the long-term effects of newer antiepileptic drugs on cognition and behavior when used in pregnancy and lactation.

ANTI-INFECTIVE DRUGS

Antihelminthics: intestinal antifilarials, antischistosomes and antitrepanematode drugs

Mebendazole

Mebendazole is a broad spectrum antihelminthic agent effective in the treatment of ascariasis, enterobiasis, trichuriasis and hookworm disease. It is embryotoxic and teratogenic in rats, and is therefore not recommended for use during pregnancy.

Albendazole

The observation of limb reduction defects at all doses in one animal study, potential for higher plasma concentrations of the metabolite if consumed with a fatty meal, and limited human pregnancy data all suggest that use of albendazole during pregnancy is not recommended. Data on the safety of albendazole in breastfeeding are lacking.

Praziquantel

Praziquantel is not a teratogen in animals, but there are few human data. Recent data indicate that the agent may be mutagenic and carcinogenic in humans, especially in developing countries where infections of trematodes and cestodes are frequent and multiple treatment courses may often need to be prescribed. Because of this potential toxicity, the use of praziquantel during pregnancy should be reserved for those cases in which the parasite is causing clinical illness or public health problems.

Antibacterials: betalactam drugs, other antibacterials, antileprosy drugs, antituberculosis drugs, antifungal drugs and antiviral drugs (antiherpes and antiretroviral)

Tetracycline

Tetracycline is contraindicated during pregnancy. This broad spectrum antibiotic crosses the placenta, chelates calcium and is deposited in the developing teeth and bones of the fetus. The effects on bone are minimal, but discoloration of the teeth and enamel hypoplasia can occur from the end of the first trimester. Staining of the permanent teeth is most likely when tetracyclines are administered after 24 weeks' gestation.

Ciprofloxacin

Quinolone treatment in developing adolescents of several animal species is associated with acute arthropathy of the weight-bearing joints. A recent study examining the effect of intrauterine exposure to quinolones suggested that the use of ciprofloxacin during the first trimester of pregnancy is not associated with

an increased risk of fetal malformations or musculoskeletal problems. Long-term follow-up is required to exclude subtle cartilage and bone damage.

Aminoglycosides

Except for eighth cranial nerve damage, no reports of congenital defects caused by streptomycin have been found. The Collaborative Perinatal Project⁶ monitored 50,282 mother-child pairs, 135 of whom had first trimester exposure to streptomycin. For use any time during pregnancy, 355 exposures were recorded. In neither group was evidence found to suggest a relationship to large categories of major or minor malformations or to individual defects. Aminoglycoside antibiotics have no detectable teratogenic risk for structural defects. The study also concluded that the risk of deafness after *in utero* aminoglycoside exposure was small. Streptomycin is compatible with breastfeeding.

Chloramphenicol

Chloramphenicol should be avoided in late pregnancy and during labor because of the potential for the 'gray baby syndrome' in newborns. The syndrome usually starts 2–9 days after therapy is begun and causes vomiting, suck refusal, rapid irregular respiration, abdominal distension followed by flaccidity, an ashen gray color and hypothermia. About 40% of affected neonates die of circulatory collapse on or about the 5th day. Its use in pregnancy should be confined to life-threatening conditions, when no alternative is available.

Nitrofurantoin

Nitrofurantoin may be administered in pregnancy, but should be avoided near term. Low

levels of glutathione may predispose the fetus to hemolytic anemia if it is exposed to nitrofurantoin shortly before birth.

Vancomycin

Vancomycin is a bactericidal antibiotic with a fetal ototoxic effect. It acts mainly by inhibiting cell wall synthesis and inhibiting RNA synthesis in bacterial cytoplasmic membranes. It should be avoided unless benefit outweighs potential risk.

Trimethoprim

Trimethoprim inhibits the reduction of dihydrofolate to tetrahydrofolate and readily crosses the placenta appearing in measurable amounts in fetal blood. The use of trimethoprim in pregnancy was associated with an approximate quadrupling of the risk of cardiovascular defects and/or an oral cleft. Risk was increased with use during the second and third months after the last menstrual period but not before or after this time. It is advisable to avoid trimethoprim in the first trimester unless benefit outweighs potential risk, and administration, if prescribed, must always be accompanied with folic acid.

Antifungal drugs

Griseofulvin

Griseofulvin is a systemic agent used to treat fungal infections of the skin, hair and nails. It is a known teratogen in laboratory animals and crosses the human placenta. Griseofulvin use is contraindicated during pregnancy, and pregnancy should be avoided for 1 month after treatment. Men should not try to father children within 6 months of treatment.

Ketoconazole

Ketoconazole is used in systemic mycoses, serious chronic resistant mucocutaneous candidiasis, gastrointestinal mycoses, chronic resistant vaginal candidiasis and resistant dermatophyte infections of skin or fingernails. It inhibits placental microsomal aromatase and cytochrome P450. Although it has been used in some pregnant women without complications, it should be avoided during pregnancy as there is insufficient information to confirm its safety.

Antiprotozoal drugs: antiamebic and antimalarial drugs

Metronidazole

Most of the published evidence now suggests that metronidazole does not present a significant risk to the fetus. A possible small risk for cleft lip with or without palate abnormalities has been reported, but the validity and the clinical significance of this finding is questionable. Metronidazole is contraindicated during the first trimester in patients with trichomoniasis or bacterial vaginosis⁹. The American College of Obstetricians and Gynecologists (ACOG) recommends that clindamycin (orally or intravaginally) be used during the first trimester for symptomatic bacterial vaginosis⁹. The use of metronidazole for trichomoniasis or vaginosis during the second and third trimesters is acceptable, as either a single 2-g oral dose or a 7-day course of 750–1000 mg/day in divided doses. For other indications, metronidazole can be used during pregnancy if no other alternatives with established safety profiles are available. In these cases, the patient should be counseled about the potential risks and informed consent obtained before initiating therapy.

Chloroquine

A 1985 report¹⁰ summarized the results of 169 infants exposed *in utero* to 300 mg of chloroquine base once weekly throughout pregnancy. The control group consisted of 454 non-exposed infants. Two study group infants had anomalies (tetralogy of Fallot and congenital hypothyroidism) compared with four in the control group. Based on these data, the authors concluded that chloroquine is not a major teratogen, but a small increase in birth defects could not be excluded. The amount of chloroquine excreted into milk is not considered to be harmful to a nursing infant.

Quinine

Newer agents have effectively replaced quinine to treat malaria. Although no increased teratogenic risk can be documented, its use during pregnancy should be avoided. Quinine is compatible with breastfeeding.

Antituberculous drugs

Rifampicin

No controlled studies have linked the use of rifampicin with congenital defects. Several reviews¹¹⁻¹³ have evaluated the available agents for treatment of tuberculosis during pregnancy. All concluded that rifampicin was not a proven teratogen and recommended use of the drug with isoniazid and ethambutol if necessary. The American Academy of Pediatrics¹⁴ considers rifampicin to be compatible with breastfeeding.

Ethambutol

No congenital defects are linked to ethambutol. The literature^{13,15,16} supports the safety of

ethambutol in combination with isoniazid and rifampicin during pregnancy. Ethambutol is compatible with breastfeeding.

ADRENOCORTICAL STEROIDS

The adrenal cortex synthesizes two classes of steroids: the corticosteroids (glucocorticoids and mineralocorticoids) having 21 carbon atoms and the androgens which have 19. Cortisone is the main glucocorticoid, and aldosterone is the main mineralocorticoid. Glucocorticoids are administered in multiple formulations for disorders that share an inflammatory or immunological basis. Except in patients receiving replacement therapy for adrenal insufficiency, glucocorticoids are neither specific nor curative, but rather are considered palliative because of their anti-inflammatory and immunosuppressive actions.

Prednisolone is the biologically active form of prednisone. The placenta can oxidize prednisolone to inactive prednisone or even less active cortisone. A study of 229,101 patients exposed to prednisolone, prednisone and methyl-prednisolone during the first trimester failed to show any association between these agents and congenital defects¹⁷. When prednisolone was used throughout the pregnancy, cataracts in the newborn occurred in rare instances. At maternal doses of 20 mg, the infant would be exposed to minimal amounts of steroid. At higher doses, however, mothers are advised to wait at least 4 hours after a dose before nursing their infants.

Betamethasone use for therapy of preterm labor is associated with decreases in respiratory distress syndrome, periventricular leukomalacia and intraventricular hemorrhage in preterm infants. However, this drug can precipitate myasthenic crisis in patients with myasthenia gravis, induce hyperglycemia and rarely a hypertensive crisis. Single courses of betamethasone have no effects on the fetus, but multiple courses have been associated

with lower birth weights and reduced head circumference at birth¹⁸⁻²⁰. Follow-up studies have not shown any differences in cognitive and psychosocial development when compared with controls²¹⁻²³. Hydrocortisone and its inactive precursor cortisone present small risks to the human fetus. These corticosteroids produce dose-related teratogenic and toxic effects in genetically susceptible experimental animals, which consist of cleft palate, cataracts, spontaneous abortion, IUGR and polycystic kidney disease.

Although extensive data^{24,25} support no adverse effects in the vast majority of human pregnancies, adverse outcomes have been observed and may have been caused by corticosteroids. Moreover, the decrease in birth weight and a small increase in the incidence of cleft lip with or without cleft palate are supported by large epidemiologic studies. Because benefits of corticosteroids far outweigh fetal risks, these agents should not be withheld if the mother's condition necessitates their use. The mother, however, should be informed of the risks, so she can actively participate in the decision regarding whether to use these agents during her pregnancy.

IMMUNOSUPPRESSIVE DRUGS

Azathioprine

Azathioprine is a 6-mercaptopurine derivative which acts as a 'steroid-sparing' agent, suppressing cell-mediated hypersensitivity and altering antibody production. Use of azathioprine in pregnant patients with renal transplant, systemic lupus erythematosus and inflammatory bowel disease is extensive. Current evidence indicates that maternal use of azathioprine is not associated with an increased risk of impaired fetal immunity, growth retardation and prematurity. In children followed for up to 20 years, no increase in congenital abnormalities or subsequent problems such

as childhood malignancy has been noted. The information on breastfeeding while taking azathioprine is without consensus. Despite little or no drug being found in breast milk, most rheumatologists advise avoidance of azathioprine if possible, or counsel against breastfeeding because of theoretical risks of immune suppression of the neonate.

Cyclosporine

Based on relatively small numbers, the use of cyclosporine during pregnancy apparently does not pose a major risk to the fetus. No pattern of defects has emerged in the few newborns with anomalies. Skeletal defects, other than a single case of osseous malformation, have not been observed. The disease process *per se* for which cyclosporine is indicated makes these pregnancies high risk and subject to numerous potential problems, of which the most common is growth retardation, and this is probably more closely related to the mother's disease rather than to her drug therapy. Nonetheless, a contribution from cyclosporine and corticosteroids cannot be excluded. Cyclosporine is contraindicated during breastfeeding due to its potential for immune suppression and neutropenia, unknown effect on growth, and possible association with carcinogenesis.

CYTOTOXIC DRUGS

These drugs exert their effects mainly on rapidly dividing cells, and hence are most dangerous at the stage of organogenesis. The alkylating agents cyclophosphamide and chlorambucil, and the folic acid antagonist methotrexate all are teratogenic and all are contraindicated in pregnancy. The risk of congenital abnormalities in cyclophosphamide-exposed children ranges between 16 and 22%, but its use may be contemplated later in pregnancy if the mother's disease is life

threatening. Methotrexate should be discontinued at least 3 months prior to conception and folic acid (5mg) supplementation given preconceptionally¹⁰.

CARDIOVASCULAR DRUGS

Antiangina drugs

Nitroglycerin

The use of nitroglycerin during pregnancy does not appear to present a risk to the fetus. However, the number of women treated during pregnancy is limited, especially during the first trimester. With the smaller doses reported, transient decreases in the mother's blood pressure may occur, but these do not appear to be sufficient to jeopardize placental perfusion. Nitroglycerin appears to be a safe, effective, rapid-onset, short-acting tocolytic agent. The use of transdermal nitroglycerin patches is also effective when longer periods of tocolysis are required.

Antiarrhythmic drugs

Amiodarone

Amiodarone is an iodine-rich antiarrhythmic drug with proven benefit in the treatment of patients with ventricular and atrial arrhythmias. It can reach the fetus by transplacental passage and induce fetal hypothyroidism. It inhibits the conversion of thyroxine to triiodothyronine in most tissues. It may also inhibit thyroid hormone synthesis and secretion, causing hypothyroidism in 5–25% of patients²⁶. Transplacental exposure to amiodarone may be associated with neurotoxicity. When compared with controls, amiodarone-exposed toddlers showed expressive language skills relatively poorer than their verbal skills²⁷. One amiodarone-exposed toddler exhibited global

developmental delay. Amiodarone-exposed older children had well developed social competence, favorable global IQ scores but exhibited problems with reading comprehension, written language and arithmetic, a picture reminiscent of the non-verbal learning disability syndrome²⁸. In another report, normal psychomotor development was observed in two patients with full-scale IQ score, and verbal and performance IQ scores within normal range. However, these data need validation by larger studies. In conclusion, drug therapy of cardiovascular rhythm disorders should be avoided during the first trimester of pregnancy if possible, and drugs with the longest record of safety should be used as first-line therapy. Conservative therapies should be used when appropriate.

Digoxin

Of 229,101 completed pregnancies studied between 1985 and 1992, 34 newborns were exposed to digoxin during the first trimester¹⁷. One (2.9%) major birth defect was observed (one expected), an oral cleft. Although the number of exposures is small, these data are supportive of previous experience for a lack of association between the drug and congenital defects. Digoxin is compatible with breastfeeding.

ANTIHYPERTENSIVE DRUGS

Beta-adrenergic antagonists

Beta-adrenergic antagonists have fewer side-effects than most antihypertensives, but their safety in pregnancy is not so well established. Some studies found no adverse effects on the outcome of pregnancy, while others described a variety of fetal and neonatal complications²⁹. The major concern is that if these drugs are used before 28 weeks' gestation, they may increase the risk of IUGR. Later complications

include bradycardia, hypotension, hypoglycemia and respiratory distress. However, many studies suggest that they are safe antihypertensives for use in the third trimester. If treatment of hypertension is required before 28 weeks, methyldopa should be the first drug of choice.

Angiotensin converting enzyme inhibitors

This group of drugs are orally active inhibitors of angiotensin converting enzyme, which is responsible for conversion of inactive angiotensin I to the potent pressor peptide angiotensin II. These drugs have been associated with prolonged renal failure and hypotension in the newborn³⁰, decreased skull ossification, hypocalvaria and renal tubular dysgenesis. In addition, there are several case reports of IUGR, oligohydramnios, patent ductus arteriosus and neonatal hypotension. The use of these drugs in the first trimester is not thought to produce structural malformations, so it is acceptable to cease treatment early in pregnancy and not necessarily preconception.

Loop diuretics (furosemide)

There is an association between use of furosemide in the first trimester and hypospadias. Furosemide is considered safe in breastfeeding. Its use is not recommended in the treatment of pre-eclampsia due to intravascular volume depletion.

Thiazide diuretics

Use of thiazides and related diuretics in the first trimester does not indicate that these agents are teratogenic. However, the Collaborative Perinatal Project⁶ found an increased risk of defects when diuretics were used during the first trimester in women with cardiovascular

disorders, but causal relationships cannot be inferred from these data without independent confirmation. Bendroflumethiazide, chlorthalidone, chlorothiazide and hydrochlorothiazide are compatible with breastfeeding

Spirolactone is a competitive antagonist of aldosterone at receptor sites in the distal renal tubules, causing a moderate salt and water diuresis with reduced loss of potassium and hydrogen. Spirolactone also exhibits antiandrogenic effects, probably through competitive inhibition at the level of testosterone, dihydrotestosterone and androstenedione receptors. These properties underlie its successful use in the treatment of idiopathic hirsutism. These antiandrogenic effects were observed in spironolactone-exposed male animal fetuses born with anomalies of external genitalia³¹. Its use in pregnancy is contraindicated, and if diuretics are necessary another agent is preferable. It is also used for the treatment of hyperaldosteronism, where amiloride or potassium supplements may be alternatives in pregnancy.

ANTITHROMBOTIC DRUGS

Warfarin

Warfarin is a form of coumarin with vitamin K antagonist action. Its use in pregnancy is associated with a high incidence of fetal loss, congenital malformations and physical disability. Exposure to the drug between the 6th and 9th weeks of gestation is associated with defective ossification of bone resulting in nasal hypoplasia and chondrodysplasia punctata. On a molecular level, vitamin K inhibitors may alter calcium binding for several proteins, affecting bone ossification and causing the characteristic bony abnormalities of the 'fetal warfarin' syndrome. The syndrome constitutes skeletal defects (nasal hypoplasia and stippled epiphyses), limb hypoplasia (particularly distal digits), low birth weight (<10th centile), hearing loss and ophthalmic anomalies. The use of

warfarin in the second and third trimester is associated with serious complications, mainly central nervous system abnormalities thought to be due to brain microhemorrhages. The defects include dorsal midline dysplasia (agenesis of corpus callosum and Dandy-Walker malformations) or ventral midline dysplasia (optic atrophy), mental retardation, delayed development, seizures and microcephaly. The risk of teratogenicity with warfarin led to the recommendation that heparin be substituted for the treatment and prophylaxis of venous thromboembolism. However, heparin is not as effective as warfarin in preventing arterial thromboembolism in women with artificial heart valves or mitral disease with arterial fibrillation. In these situations, the risk of thrombosis may exceed the risks of warfarin use, and warfarin therefore may be indicated. It should, however, be used with great caution and close monitoring of both the mother and fetus.

Heparin

Heparin is the anticoagulant of choice from the fetal perspective, as it does not cross the placenta. Two major side-effects that can occur with heparin treatment are heparin-induced thrombocytopenia and osteoporosis. Two types of thrombocytopenia occur with heparin treatment. Non-immune heparin-associated thrombocytopenia is associated with a mild reduction in platelet counts and occurs 2–5 days after heparin injection. Immune thrombocytopenia, on the other hand, occurs due to IgG antiplatelet antibodies, occurring 3–4 weeks after therapy and increasing the risk of thrombus formation.

LIPID-LOWERING AGENTS

Simvastatin

Based on the animal data and limited human experience, exposure to simvastatin during

early pregnancy does not appear to present a significant fetal risk. The outcomes reported are within those expected in a non-exposed population. However, because the interruption of cholesterol-lowering therapy during pregnancy should have no apparent effect on the long-term treatment of hyperlipidemia, simvastatin should not be used during pregnancy. Women taking this agent before conception should ideally stop the therapy before becoming pregnant and certainly on recognition of pregnancy. Accidental use of the drug during gestation, though, apparently has no known consequences for the fetus. Because of the potential for adverse effects in the nursing infant, the drug should not be used during lactation.

HORMONES AND OTHER ENDOCRINE DRUGS AND CONTRACEPTIVES

Androgens

Danazol

Danazol is a testosterone derivative and a weak androgen, used for the treatment of endometriosis, menstrual disturbances, immune thrombocytopenic purpura, classic hemophilia, Christmas disease and α 1 antitrypsin deficiency. Reports suggest virilization of the external genitalia of female fetuses exposed to the drug during pregnancy producing fused labia and clitoral hypertrophy³². It should be avoided in pregnancy.

Hormonal contraceptives

Because oral contraceptives are primarily combination products, it is difficult to separate entirely the fetal effects of the contained progestogens and estrogens. Except for the modified development of sexual organs, no firm evidence has appeared that establishes a causal

relationship between oral contraceptives and various congenital anomalies. The acronym VACTERL (vertebral, anal, cardiac, tracheal, esophageal, renal or radial, and limb) was used initially to describe fetal malformations produced by oral contraceptives or the related hormonal pregnancy test preparations (no longer available in the US). The Population Council³³ estimates that, even if the study findings for VACTERL malformations are accurate, such abnormalities occur in only 0.07% of pregnancies exposed to oral contraceptives. Some later reviewers³⁴ have concluded that the risk to the fetus for non-genital malformations after *in utero* exposure to these agents is small, if indeed it exists at all.

In contrast, the effect of estrogens and some synthetic progestogens on the development of the sexual organs is well established. Masculinization of the female infant has been associated with norethindrone, norethynodrel, hydroxyprogesterone, medroxyprogesterone and diethylstilbestrol. The incidence of masculinization of female infants exposed to synthetic progestogens is approximately 0.3%. Pseudohermaphroditism in the male infant is not a problem, because of the low doses of estrogen employed in oral contraceptives.

Progestogens

Although many of the progestagens used as contraceptive agents, such as norethisterone and levonorgestrel, are 19-nortestosterone derivatives and have mild androgenic properties with a potential to produce virilization of a female fetus³⁵, they are unlikely to do so owing to the small amounts present.

INSULIN AND OTHER ANTIDIABETIC AGENTS

Metformin may be beneficial for decreasing the incidence of fetal and/or newborn morbidity

and mortality in developing countries where the proper use of insulin is problematic, as insulin is still the treatment of choice for this disease. Moreover, insulin, unlike metformin, does not cross the placenta and, thus, eliminates the additional concern that the drug therapy itself is adversely affecting the fetus. Carefully prescribed insulin therapy provides better control of the mother's blood glucose, thereby preventing fetal and neonatal complications. High maternal glucose levels, as may occur in un- or poorly treated diabetes mellitus, are closely associated with a number of maternal and fetal adverse effects, including fetal structural anomalies if the hyperglycemia occurs early in gestation. To prevent this, most experts, including ACOG, recommend that insulin be used for types I and II diabetes occurring during pregnancy and, if diet therapy alone is not successful, for gestational diabetes.

THYROID HORMONE AND OTHER ANTITHYROID DRUGS

Propylthiouracil

Of 229,101 completed pregnancies between 1985 and 1992, 35 newborns were exposed to propylthiouracil (PTU) during the first trimester¹⁷. One (2.9%) major birth defect was observed (one expected), a case of hypospadias (none expected). A 1992 study reported the retrospective evaluation of hyperthyroid pregnancy outcomes treated with either PTU ($n = 99$) or methimazole ($n = 36$)³⁶. Three (3.0%) defects were observed in those exposed to PTU (ventricular septal defect, pulmonary stenosis, patent ductus arteriosus in a term infant), whereas one newborn (2.8%) had a defect (inguinal hernia) in the methimazole group. No scalp defects were observed. In comparison with other antithyroid drugs, PTU is considered the drug of choice for the medical treatment of hyperthyroidism

during pregnancy, and is compatible with breastfeeding³⁷.

Methimazole and carbimazole

A specific pattern of rare congenital malformations secondary to exposure to methimazole during the first 7 weeks of gestation is reported that consists of some or all of the following: scalp or patchy hair defects; choanal atresia; esophageal atresia with tracheoesophageal fistula; minor facial anomalies; hypoplastic or absent nipples; and psychomotor delay. These defects may indicate a phenotype for methimazole embryopathy. Because of the possible association with aplasia cutis and other malformations, and the passage of methimazole into breast milk, PTU is the drug of choice for the medical treatment of hyperthyroidism during pregnancy. Both methimazole and carbimazole are compatible with breastfeeding.

PSYCHOTHERAPEUTIC DRUGS

Antipsychotic drugs

Lithium

Lithium carbonate may be administered to pregnant women for treatment of the manic phase in manic-depressive psychosis (bipolar disorder). The precise mechanism of action is unknown, but it is thought to be due to altered ion transport or inhibition of adenylyl cyclase, influencing nerve excitation, synaptic transmission and neuronal metabolism in the CNS. Lithium is associated with an increased incidence of fetal abnormalities. Since the 1960s an international Register of Lithium Babies has collected information about lithium-exposed children in the first trimester of pregnancy³⁸. It is estimated that 7.8% of lithium-exposed embryos develop abnormalities. Early data showed that the cardiovascular system is the most affected, with Ebstein anomaly affecting one-third of lithium-exposed embryos. While

initial information regarding the teratogenic risk of lithium treatment was derived from biased retrospective reports, more recent epidemiological data indicate that the teratogenic risk of first trimester lithium exposure is lower than previously suggested. The clinical management of women with bipolar disorder who have childbearing potential should be modified using this revised risk estimate. If lithium is used for prophylaxis, it is advisable to discontinue it during the first trimester, unless its withdrawal would jeopardize the woman or her pregnancy. During pregnancy, the smallest dose possible for acceptable therapeutic effects should be used. Frequent small dosages avoid larger fluctuations in maternal plasma concentrations, and each dosage should not exceed 300 mg with even spacing throughout the 24-hour period. Plasma levels should be monitored every 3–7 days.

Drugs used in depressive disorders

Tricyclic antidepressants and fluoxetine

Tricyclic antidepressants and fluoxetine are the first-line choices in the management of depression. Tricyclic antidepressants have a long history of use without increasing teratogenic risk in pregnant women. Fluoxetine has been studied in prospective trials without evidence for a higher incidence of malformations or other teratogenicity. Doses of tricyclic antidepressants may need to be higher in pregnancy due to increased hepatic metabolism. Where appropriate, to avoid withdrawal symptoms in the neonate, antidepressants should be slowly withdrawn or reduced to the minimum dose prior to delivery.

Drugs used in generalized anxiety and sleep disorders

Benzodiazepines are contraindicated in the first trimester. Diazepam and its metabolite, desmethyl diazepam, freely cross the placenta

and accumulate in the fetal circulation with newborn levels about 1–3 times greater than maternal serum levels. Transfer across the placenta occurs as early as 6 weeks' gestation, suggesting that diazepam accumulates in the fetal circulation and tissues during organogenesis. In 1427 malformed newborns compared to 3001 controls, first trimester use of tranquilizers (diazepam most common) was associated with inguinal hernia, cardiac defects and pyloric stenosis³⁹. Second trimester exposure was associated with hemangiomas and cardiac and circulatory defects.

The effects of benzodiazepines, including diazepam, on the human embryo and fetus are controversial. However, the risk appears to be low, if indeed diazepam and the other agents do cause birth defects. Continuous use during gestation results in neonatal withdrawal and a dose-related syndrome is apparent if diazepam is used close to delivery. Consequently, if the maternal condition requires the use of diazepam during pregnancy, the lowest possible dose should be prescribed. Abrupt discontinuation of benzodiazepines should be avoided, as severe maternal withdrawal symptoms (physical and psychological) may occur. Fetal withdrawal, such as that observed with narcotics, has not been reported, but should be considered.

Use during labor is considered safe as long as the dose does not exceed more than 30–40 mg and the drug is not used over a long period of time. Neonatal complications from benzodiazepines include floppy infant syndrome with hypotonia, lethargy, sucking difficulties or withdrawal syndrome with IUGR, tremors, irritability, hypertonicity, diarrhea/vomiting and vigorous sucking.

DRUGS ACTING ON THE RESPIRATORY TRACT

Theophyllines

The Collaborative Perinatal Project⁶ monitored 193 mother-child pairs with first trimester

exposure to theophylline or aminophylline. No evidence was found for an association with malformations. Theophylline withdrawal in a newborn exposed throughout gestation has been reported. Apneic spells developed at 28 hours after delivery and became progressively worse over the next 4 days⁴⁰. Therapy with theophylline resolved the spells. Except for the precaution that theophylline may cause irritability in the nursing infant, the American Academy of Pediatrics¹⁴ considers the drug to be compatible with breastfeeding.

RADIOACTIVE IODINE

Radioactive iodine therapy is contraindicated in pregnancy since the uptake by fetal thyroid results in thyroid ablation and hypothyroidism. Pregnancy should be avoided for at least 4 months after treatment with radioactive iodine therapy and investigations using ¹³¹I in view of the theoretical risk of chromosomal damage and genetic abnormalities.

VITAMINS

Retinoids

Acitretin and isotretinoin

Acitretin and isotretinoin are synthetic vitamin A derivatives. Acitretin, a metabolite of etretinate, is an oral preparation used for the treatment of severe resistant or complicated psoriasis and some of the congenital disorders of keratinization. Isotretinoin reduces sebum secretion and in its oral form is used for the treatment of nodulo-cystic and conglobate acne and severe antibiotic-resistant acne. Teratogenic effects have been reported to occur in up to 25% of babies born to mothers who took retinoids. The embryopathy includes CNS defects (hydrocephalus, optic nerve blindness, retinal defects, microphthalmia, posterior fossa defects, and cortical and cerebellar

defects), craniofacial defects (microtia or anotia, low-set ears, hypertelorism, depressed nasal bridge, microcephaly, micrognathia and agenesis or stenosis of external ear canals), cardiovascular defects (transposition of great vessels, tetralogy of Fallot and ventricular or atrial septal defects), thymic defects (ectopia and hypoplasia or aplasia) and miscellaneous defects (limb reduction, decreased muscle tone, spontaneous miscarriage and behavioral abnormalities). Isotretinoin is eliminated from the body within 4 weeks of stopping treatment, but acitretin is eliminated more slowly and pregnancy should be avoided for 2 years after a course of the drug. Fetal abnormalities have not been associated with topical retinoids, but it is advisable to avoid their use in pregnancy and ensure women use adequate contraception.

VACCINES IN PREGNANCY

Live attenuated vaccines are generally avoided in pregnancy. All killed vaccines are safe in pregnancy. Vaccines that give passive immunization are safe in the preconception period and during pregnancy. A list of vaccines and their use is shown in Table 4.

CONCLUSION

Current practice of prescribing in the preconceptional period is similar to that in patients who are not planning for a pregnancy. With the limitations in the available data regarding safety; however, the possibility of serious detrimental effects to the fetus, many of which may not be even identified in the fetal

Table 4 Usage of vaccines in pregnancy and preconception. (Adapted from the CDC guideline⁴¹)

Hepatitis A	The safety of hepatitis A vaccination during pregnancy has not been determined; however, because hepatitis A vaccine is produced from inactivated (hepatitis A virus), the theoretical risk to the developing fetus is expected to be low. The risk associated with vaccination should be weighed against the risk for hepatitis A in pregnant women who may be at high risk for exposure to hepatitis A virus
Hepatitis B	Pregnancy is not a contraindication to vaccination. Limited data indicate no apparent risk for adverse events to developing fetuses when hepatitis B vaccine is administered to pregnant women. Current vaccines contain non-infectious HBsAg and should cause no risk to the fetus. Pregnant women who are identified as being at risk for HBV infection during pregnancy (e.g. having more than one sex partner during the previous 6 months, been evaluated or treated for a sexually transmitted disease, recent or current injection drug use, or having had an HBsAg-positive sex partner) should be vaccinated
Human papillomavirus (HPV)	Quadrivalent HPV vaccine is not recommended for use in pregnancy. If a woman is found to be pregnant after initiating the vaccination series, the remainder of the three-dose regimen should be delayed until after completion of the pregnancy. If a vaccine dose has been administered during pregnancy, no intervention is needed
Influenza (inactivated)	Vaccination with inactivated influenza vaccine is recommended for persons who are at increased risk for severe complications from influenza, such as women who will be pregnant during the influenza season
Influenza (LAIV)	Should not be used in pregnancy

continued

Table 4 *continued*

MMR	<p>Measles-mumps-rubella (MMR) vaccine and its component vaccines should not be administered to women known to be pregnant. Because a risk to the fetus from administration of these live virus vaccines cannot be excluded for theoretical reasons, women should be counseled to avoid becoming pregnant for 28 days after vaccination with measles or mumps vaccines or MMR or other rubella-containing vaccines</p> <p>If vaccination of an unknowingly pregnant woman occurs or if she becomes pregnant within 4 weeks after MMR vaccination, she should be counseled about the theoretical basis of concern for the fetus; however, MMR vaccination during pregnancy should not be regarded as a reason to terminate pregnancy</p>
Pneumococcal (PPV23)	The safety of pneumococcal polysaccharide vaccine during the first trimester of pregnancy has not been evaluated, although no adverse consequences have been reported among newborns whose mothers were inadvertently vaccinated during pregnancy
Polio (IPV)	Although no adverse effects of IPV have been documented among pregnant women or their fetuses, vaccination of pregnant women should be avoided on theoretical grounds. However, if a pregnant woman is at increased risk for infection and requires immediate protection against polio, IPV can be administered in accordance with the recommended schedules for adults
Rubella	Rubella-susceptible women who are not vaccinated because they state they are or may be pregnant should be counseled about the potential risk for congenital rubella syndrome and the importance of being vaccinated as soon as they are no longer pregnant
Tetanus, diphtheria and pertussis (Tdap)	Pregnancy is not a contraindication for use of Tdap. Data on safety, immunogenicity and the outcomes of pregnancy are not available for pregnant women who receive Tdap. When Tdap is administered during pregnancy, transplacental maternal antibodies might protect the infant against pertussis in early life. They also could interfere with the infant's immune response to infant doses of Tdap, and leave the infant less well protected against pertussis
Varicella	The effects of the varicella virus vaccine on the fetus are unknown; therefore, pregnant women should not be vaccinated. Non-pregnant women who are vaccinated should avoid becoming pregnant for 1 month following each injection. For susceptible persons, having a pregnant household member is not a contraindication to vaccination. If vaccination of an unknowingly pregnant woman occurs or if she becomes pregnant within 4 weeks after varicella vaccination, she should be counseled about the theoretical basis of concern for the fetus; however, varicella vaccination during pregnancy should not be regarded as a reason to terminate pregnancy
BCG	Although no harmful effects to the fetus have been associated with BCG vaccine, its use is not recommended during pregnancy

continued

Table 4 continued

Japanese encephalitis (JE)	No specific information is available on the safety of JE vaccine in pregnancy. Vaccination poses an unknown but theoretical risk to the developing fetus, and the vaccine should not be routinely administered during pregnancy. Pregnant women who must travel to an area where risk of JE is high should be vaccinated when the theoretical risks of immunization are outweighed by the risk of infection to the mother and developing fetus
Rabies	Because of the potential consequences of inadequately treated rabies exposure, and because there is no indication that fetal abnormalities have been associated with rabies vaccination, pregnancy is not considered a contraindication to postexposure prophylaxis. If the risk of exposure to rabies is substantial, pre-exposure prophylaxis might also be indicated during pregnancy
Typhoid	No data have been reported on the use of any of the three typhoid vaccines among pregnant women
Yellow fever	The safety of yellow fever vaccination during pregnancy has not been established, and the vaccine should be administered only if travel to an endemic area is unavoidable and if an increased risk for exposure exists. Infection of the fetus with YF17D apparently occurs at a low rate and has not been associated with congenital anomalies. If international travel requirements are the only reason to vaccinate a pregnant woman, rather than an increased risk of infection, efforts should be made to obtain a waiver letter from the traveler's physician. Pregnant women who must travel to areas where the risk of yellow fever is high should be vaccinated and, despite the apparent safety of this vaccine, infants born to these women should be monitored closely for evidence of congenital infection and other possible adverse effects resulting from yellow fever vaccination
Zoster (singles)	Contraindications: Zostavax should not be administered to individuals who are or may be pregnant. It is not known whether Zostavax can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. However, naturally occurring VZV infection is known to sometimes cause fetal harm. Therefore, Zostavax should not be administered to pregnant females; furthermore, pregnancy should be avoided for 3 months following vaccination

life, emphasizes the need for change of practice. In view of the above-mentioned as well as unforeseen dangers, prescribing in the preconceptional period should in the future be on the same grounds as prescribing for pregnancy.

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