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Anti-infective Agents

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2.6

Infections may be hazardous to the health of the mother, the course of pregnancy, and the unborn child. They can lead to premature labor or premature rupture of membranes and thereby increase the risk for spontaneous abortion and prematurity. Furthermore, certain germs can pass to the unborn child and harm it directly. Therefore, an anti-infective treatment which should be both effective and safe for the mother and the unborn child is often required. The use of penicillins and older cephalosporins is well documented and considered to be safe. Consequently, they are the drug of choice during pregnancy. In selected cases of bacterial resistance or intolerance to first-line antibiotics, other anti-infective agents might be recommended. Especially for life-threatening infections, a therapy with not so well-tried agents might be needed. The potential benefit of treatment in such cases most often outbalances the potential risk for the unborn child.

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2.6.1 Penicillins and β-lactamase inhibitors

Penicillins belong to the β-lactam antibiotics. They inhibit cell-wall synthesis in bacteria and have bactericidal properties. The group of penicillins includes *amoxicillin*, *ampicillin*, *azidocillin*, *bacampicillin*, *benzylpenicillin* (*penicillin G*), *carbenicillin*, *cloxacillin*, *dicloxacillin*, *flucloxacillin*, *mezlocillin*, *oxacillin*, *phenoxymethylpenicillin* (*penicillin V*), *piperacillin*, *pivmecillinam*, *propicillin*, and *ticarcillin*.

Penicillins cross the placenta and can be detected in the amniotic fluid. In thousands of studied pregnancies over the past decades, no indications were seen to show that treatment with penicillins is embryo- or fetotoxic (e.g. Cooper 2009, Jepsen 2003, Dencker 2002, Czeizel 2000a, 2001a). Nevertheless, a few studies have discussed an association with cleft palate and maternal use of amoxicillin or ampicillin (Lin 2012, Puhó 2007). Lin (2012) discussed an absolute cleft risk of 2–4 per 1,000, a quite modest increase compared to the background risk. Mølgaard-Nielsen (2012) could not find an increased risk for oral clefts after intrauterine amoxicillin exposure; but they saw an increased risk for cleft palate after pivmecillinam exposure in the third month. In one investigation of more than 2,000 pregnant women exposed to pivmecillinam – more than 500 of them in the first trimester – found neither an increased malformation rate nor other abnormalities in the newborns (Vinther Skriver 2004). Pregnant women who are treated with penicillin for syphilis may develop the Jarisch-Herxheimer reaction – a febrile reaction, often with headache and myalgia. Fetal monitoring is recommended in such cases, as uterine contractions may occur (Myles 1998). The carboxypenicillins carbenicillin and ticarcillin also did not show any adverse effects in animal experiments, but experience in humans is very limited.

Clavulanic acid, *sulbactam*, and *tazobactam* are β-lactamase inhibitors that are prescribed in combination with a penicillin. Fixed combinations are for example, clavulanic acid plus ampicillin, sulbactam plus ampicillin and tazobactam plus piperacillin. Sultamicillin is an orally available prodrug of ampicillin and sulbactam that is rapidly cleaved in the body into both components. So far as studied, β-lactamase inhibitors cross the placenta and reach the fetus in relevant quantities. Malformations have not been observed in animal experiments or in humans (Berkovitch 2004, Czeizel 2001a).

In a large, randomized multicenter trial, the prenatal use of ampicillin and clavulanic acid was associated with a significant increase in the occurrence of neonatal necrotizing enterocolitis (Kenyon 2001); other studies could not confirm this concern (Ehsanipoor 2008).

The clearance of penicillin and β-lactamase inhibitors is increased during pregnancy, leading to a discussion that it might be necessary to adjust dose and administration intervals during pregnancy (Heikkilä 1994). Muller (2008) failed to observe any relevant differences in the pharmacokinetics when studying 17 women who received amoxicillin for premature rupture of membranes.

Recommendation. Penicillins belong to the antibiotics of choice during pregnancy. Where bacterial resistance studies are indicated, penicillins may be combined with clavulinic acid, sulbactam, or tazobactam.

2.6.2 Cephalosporins

Like penicillins, cephalosporins belong to the β-lactam antibiotics. They inhibit the cell wall synthesis of bacteria and have a bactericidal effect. Cephalosporins are classified according to their antimicrobial activity.

Cephalosporins of the first generation include *cefadroxil*, *cefazolin*, *cephalexin*, *cephalotin*, and *cephradine*. To the second generation belong *cefaclor*, *cefamandole*, *cefdinir*, *cefditoren*, *cefmetazole*, *cefotetan*, *cefotiam*, *cefoxitin*, *cefprozil*, *cefuroxime*, and the carbacephem *loracarbef* that is related to the cephalosporins. The third generation contains *cefdinir*, *cefditoren*, *cefixim*, *cefoperazone*, *cefotaxime*, *cefpodoxim*, *ceftazidime*, *ceftibuten*, *ceftizoxime*, and *ceftriaxone*. Cefepime and cefpirome are fourth generation cephalosporins. The new cephalosporins *ceftaroline* and *ceftobiprole* have been assigned to the fifth generation, and are indicated for severe infections with methicillin-resistant staphylococci (MRSA) and other multi-resistant germs.

Cephalosporins cross the placenta and are detectable in the amniotic fluid at bactericidal concentrations. Elimination in pregnant women is faster, and it may be necessary to adjust dosage (Heikkilä 1994). According to observations so far, e.g. about cefuroxim during the first trimester (Berkovitch 2000), cephalosporins do not cause teratogenic problems at therapeutic doses (Czeizel 2001b). Normal physical and mental development has been confirmed in children up to the age of 18 months, where mothers had been treated with cefuroxim during pregnancy (Manka 2000).

Recommendation. Like penicillins, cephalosporins belong to the antibiotics of choice during pregnancy. Whenever possible, well established cephalosporins should be used preferentially, e.g., cefaclor, cefalexin, and cefuroxim.

2.6.3 Carbapenems and monobactams

Like all β-lactam antibiotics, carbapenems and monobactams inhibit bacterial cell wall synthesis and thus are bactericidal. Generally, they are well tolerated and act as broad-spectrum antibiotics. The carbapenems include *doripenem*, *ertapenem*, *meropenem*, and *imipenem*. Imipenem can only be obtained in combination with *cilastin* which itself has no antimicrobic activity. Cilastin specifically inhibits the enzyme dehydropeptidase-1 and blocks the rapid degradation of imipenem. Aztreonam is the first monobactam available for clinical applications.

As far as is known, both carbapenems and monobactams cross the placenta and reach the fetus in relevant quantities (Heikkilä 1992). Animal studies and human experience do not show malformations or other undesirable effects; however, systematic investigations have not been conducted. Specifically, there are hardly any experiences in pregnancy with the newer carbapenems – doripenem and ertapenem.

Recommendation. Aztreonam, imipenem, and meropenem may be used when resistance testing indicates that they are needed. Doripenem and ertapenem should only be used in pregnancy when no alternatives are available.

2.6.4 Erythromycin and other macrolides

Pharmacology

Erythromycin and other macrolides inhibit bacterial protein synthesis and are bacteriostatic. Macrolides are primarily applied in the treatment of infections with Gram-positive germs, but are also effective against *Haemophilus influenzae* and intracellular pathogens such as chlamydia. Macrolides offer an alternative for patients with penicillin allergy.

Erythromycin is the oldest medication of this group. Its resorption can be delayed in the third trimester. Gastrointestinal side effects can lead to lower than therapeutic plasma concentrations, resulting in treatment failure (Larsen 1998). Only 5–20% of the maternal erythromycin concentration is obtained in the fetus. Therefore, erythromycin is not a sufficiently reliable drug for fetal or amniotic infections.

The newer macrolide antibiotics *azithromycin*, *clarithromycin*, *dirithromycin*, *josamycin*, *midecamycin*, *roxithromycin* and *troleandomycin* have a similar antibacterial spectrum as erythromycin, but to some degree less gastrointestinal side effects. *Spiramycin* is used for toxoplasmosis in the first trimester.

Telithromycin is the first ketolide antibiotic for clinical use. It is structurally related to erythromycin.

Toxicology

Erythromycin has always been considered a safe and effective antibiotic during pregnancy. Data on several thousand first trimester exposures do not support an association between erythromycin and congenital malformations (e.g. Czeizel 1999a). However, an analysis of the data from the Swedish Birth Registry showed a weakly significant increase in malformations in 1,844 children whose mothers took erythromycin in early pregnancy compared to offspring whose mothers used phenoxymethylpenicillin (Källén 2005a). This was based on an increased rate of cardiovascular malformations, especially ventricular and atrial septal defects. An update of the Swedish data verified an association between the use of erythromycin during early pregnancy and cardiovascular defects (Källén 2014). An increased incidence of pyloric stenosis was discussed by the same author (Källén 2005a). This observation after intrauterine exposure in the first trimester is biologically not plausible; but it should be mentioned that a link has been suggested between a neonatal treatment with erythromycin during the first two weeks and the development of pylorus stenosis (e.g. Mahon 2001). Other studies have failed to find a higher rate of septum defects, pyloric stenosis or other malformations (Bahat Dinur 2013, Lin 2013, Romøren 2012, Malm 2008, Cooper 2002, Louik 2002). In summary, the experiences argue against an increased embryo- and fetotoxic risk for erythromycin.

There are several reports of maternal hepatotoxic changes when *erythromycin estolate* was administered in the second half of pregnancy. These women developed a cholestatic icterus during the second week of treatment that abated within weeks when the treatment was discontinued, without evidence of permanent damage or signs of fetal compromise (e.g. McCormack 1977).

Azithromycin, *clarithromycin* and *roxithromycin* have also been studied in several publications without any indication of embryo- or fetotoxic effects (Bar-Oz 2012, Bar-Oz 2008, Chun 2006, Sarkar 2006, Drinkard 2000, Einarson 1998). In the case of clarithromycin, there was some

initial concern as animal experiments demonstrated teratogenic effects, and for instance, in some studies cardiovascular defects were induced in rats. Recently a Danish cohort study based on a prescription register observed an increased risk of miscarriage after clarithromycin in early pregnancy, but no increased risk for major malformations (Andersen 2013a).

Experience with *dirithromycin*, *josamycin*, *midecamycin*, *spiramycin*, and *troleandomycin* is very limited (Czeizel 2000b). Spiramycin has been used in many first trimesters for the treatment of toxoplamosis. Although these reports did not focus on a possible teratogenic effect, numerous normal births after spiramycin exposure are reassuring.

There is no published experience with the use of the ketolide *telithromycin* in the first trimester. The animal experiments did not show that this agent is teratogenic.

A local treatment with macrolides is quite safe for the fetus. Yet, because resistance develops quickly and allergies are frequent, macrolides should be used with some reservation.

Recommendation. Erythromycin, clarithromycin, azithromycin, and roxithromycin may be used in pregnancy when the resistance spectrum requires them, or in cases of an allergy to penicillin. Because of hepatotoxicity, erythomycin estolate should not be given during the second and third trimester. Spiramycin is the treatment of choice for toxoplasmosis in the first trimester. Telithromycin and other makrolides should only be given during pregnancy when no alternatives are available.

2.6.5 Clindamycin and lincomycin

Clindamycin and *lincomycin* belong to the lincosamide group. They inhibit bacterial protein synthesis and can be bactericidal or bacteriostatic depending on concentration and sensitivity. After an oral dose the resorption is almost complete. About half of the maternal concentration can be attained in the umbilical veins. There were no signs of embryo- or fetotoxic effects in several hundred pregnant women treated with lincomycin at different points in pregnancy (Czeizel 2000c, Mickal 1975). There were also no problems found for clindamycin. Pseudomembranous enterocolitis is a dangerous maternal complication of clindamycin treatment that may also happen after vaginal application.

Pregnancy complications due to bacterial vaginosis are not sufficiently preventable by vaginal clindamycin therapy (Joesoef 1999). It should be noted though, that other investigators found a reduction in late abortions and prematurity when treating several hundred patients with oral clindamycin for an abnormal vaginal flora (Ugwumadu 2003).

Recommendation. Clindamycin and lincomycin should only be used when penicillins, cephalosporins and macrolides have failed. Clindamycin should not be routinely used after dental procedures.

2.6.6 Tetracyclines

Pharmacology

The bacteriostatic effect of *tetracyclines* is based on an inhibition of the bacterial protein synthesis. These broad-spectrum antibiotics, especially tetracycline itself, form stable chelates with calcium ions. The standard agent today is *doxycycline*. *Minocycline* is especially lipophilic and displays a somewhat wider antibacterial spectrum than doxycycline. The older derivatives such as *oxytetracycline* and tetracycline are now rarely used as they are poorly resorbed.

Chlortetracycline, *demeclocycline*, and *meclocycline* are only used as local agents.

Tigecycline is a minocycline derivative that belongs to the glycylcyclines; it has a very broad-spectrum and is especially effective against multi-resistant pathogens such as MRSA.

Toxicology

Tetracyclines cross the placenta. According to current knowledge an increased risk of malformation is not expected when tetracyclines are used (Cooper 2009, Czeizel 1997). The results of a population-based case-control study suggested that oxytetracycline was associated with an increased incidence of congenital malformations (Czeizel 2000d). However, the number of cases in this study was small, and there are no other studies confirming this suspicion. A Danish cohort study found an association between oral clefts and maternal tetracycline exposure in the second month, but this result was based on only two exposed cases (Mølgaard-Nielsen 2012).

From the sixteenth week of pregnancy when fetal mineralization takes place, tetracyclines can bind to calcium ions in developing teeth and bones. In the 1950s numerous publications described the brown/yellow discoloration of teeth in children who were prenatally exposed to tetracyclines. Such dental discoloration is the only proven prenatal side effect of tetracyclines in humans. Under discussion were also enamel defects leading to an increased risk of caries, inhibition of the growth of the long bones, specifically the fibula and further, cataracts due to depositions into the lens. As doxycycline has a weaker affinity to calcium ions than the older tetracyclines, the risk appears to be lower for doxycycline exposures.

A discoloration of milk teeth is not to be expected prior to the sixteenth week of gestation. Even thereafter, at worst, only the first molars of the permanent teeth would be affected when the usual therapeutic regimens if current dosings are adhered to. A bigger risk for the described development abnormalities can possibly expected with higher tetracycline doses during the second and third trimester that are necessary, for example, in malaria treatment.

In the past, the use of tetracyclines, especially in high doses or via intravenous administration in the second half of pregnancy, has been associated with severe maternal hepatic toxicity (e.g. Lewis 1991). In most cases these were patients with kidney problems whose serum concentrations were markedly above the therapeutic range.

No untoward effects have been described in pregnant women who applied tetracyclines locally during pregnancy.

There is a lack of experience with *tigecycline*; no statement can be made about its tolerance in pregnancy.

Recommendation. All tetracyclines are contraindicated after the fifteenth gestational week. Prior to this, they are antibiotics of second choice. Doxycycline should be preferred in such cases. Inadvertent use of tetracyclines, even after the fifteenth week, is not an indication for termination of pregnancy (Chapter 1.15). If really necessary, a local application to a small area may be conducted throughout pregnancy. Tigecyclin is reserved for special situations when sufficiently tested antibiotic are not effective.

2.6.7 Sulfonamides and trimethoprim

Pharmacology

Sulfonamides have a bacteriostatic effect by inhibiting bacterial folic acid synthesis. Important representatives of this group are *sulfadiazine*, *sulfadoxine*, *sulfalene*, *sulfamerazine*, *sulfamethizole* and *sulfamethoxazole*. For local application *silver sulfadiazine* is used for burn injuries and *sulfacetamide* for eye infections.

Sulfonamides attain 50–90% of the maternal concentration in the fetus and compete with bilirubin for binding sites on albumin. Today, sulfonamides are seldom used as monotherapy because their spectrum is limited and resistance develops rapidly. Combined with a folate antagonist such as *trimethoprim* or *pyrimethamine* (Section 2.6.16), sulfonamides are indicated among others in the treatment of toxoplasmosis and malaria. The fixed combination of the sulfonamide sulfamethoxazole and trimethoprim is available as *co-trimoxazole*. Both agents in this combination are not subject to pregnancy-induced variation in clearance that would require dose modifications. Trimethoprim is effective as a monotherapy in uncomplicated urinary tract infections with sensitive pathogens.

Toxicology

To date, there are no indications that sulfonamides, trimethoprim, and their combinations have a teratogenic potential in humans (Nørgård 2001, Czeizel 1990). An embryotoxic potential has been discussed from time to time, because antagonists to folic acid can lead to malformations in animal experiments, and in humans the spontaneous incidence of neural tube defects (spina bifida) can be decreased by the administration of folic acid during early pregnancy (Chapter 2.18). The fact that human folic acid reductase is much less sensitive to trimethoprim than the bacterial enzyme, could explain that teratogenic problems have so far not been documented in humans when antibiotics with folic acid antagonists were used.

Trimethoprim has been used for many decades in pregnant women. At present, there is an ongoing discussion concerning the association between the use of folic acid antagonists and an increased risk of congenital malformations. A retrospective case-control study discusses the causal relationship between treatment with trimethoprim and other folic acid antagonists, and the development of neural tube defects, cardiovascular abnormalities, cleft lip and palate, and urinary tract anomalies (Hernandez-Diaz 2000). Authors' views on a preventative dose of multivitamin and folic acid preparations vary. Additional case-control studies, some of them with notable methodological problems, found weakly

significant evidence for the development of cardiovascular defects, urinary tract anomalies, anencephaly, limb defects, and orofacial clefts (e.g. Mølgaard-Nielsen 2012, Crider 2009, Czeizel 2001c). An increased risk for preterm birth and low birth weight has also been observed after exposure to trimethoprim/sulfamethoxazole (Santos 2011, Yang 2011). A Danish cohort study based on a prescription register found a doubling of the hazard of miscarriage after trimethoprim exposure in the first trimester (Andersen 2013b). Based on the same prescription register, an increased risk of heart and limb defects was observed after preconceptional exposure (during the 12 weeks before conception) to trimethoprim (Andersen 2013c). Beside methodological problems, such an association seems unlikely because a short-term therapy with trimethoprim does not usually lead to a relevant folic acid deficiency as a possible cause for birth defects. Trimethoprim and sulfonamides are not drugs of first choice, but they exhibit no established teratogens. According to current knowledge the teratogenic risk of a trimethoprim and sulfonamide therapy is negligible. Actually, there are no sufficiently convincing arguments to support the recommendation of an additional folic acid administration during an antibiotic therapy with the discussed medications, see Chapter 2.18.8 for additional discussion concerning folic acid usage.

Extensive, generally reassuring experiences in the use of co-trimoxazole for common urinary tract infections during pregnancy, do not include the conclusion that this medication is safe when used at a much higher dose for opportunistic infections such as a Pneumocystis pneumonia in the context of an HIV infection. So far, there have been no reports of malformations when such therapy was used in pregnant women.

There are no systematic studies about the local application of sulfonamides during pregnancy.

Neonatal toxicity

As sulfonamides compete with bilirubin for binding sites with plasma proteins, it has been argued that the risk of neonatal kernicterus is increased when sulfonamides are given at the end of gestation. With current surveillance, the danger of kernicterus is not tangible. However, a rise in bilirubin, especially in premature infants, cannot be excluded when sulfonamides have been used until birth. A Danish population-based study could not find an association between sulfamethoxzole exposure near term and an increased risk of neonatal jaundice (Klarskov 2013).

Recommendation. Sulfonamides, trimethoprim, and co-trimoxazole are antibiotics of second choice throughout pregnancy. If high dose co-trimoxazole is used for a Pneumocystis pneumonia during the first trimester, based on theoretical grounds, folic acid should be supplemented and a detailed ultrasound examination should be offered to ascertain the normal development of the fetus. If a premature birth is threatening, sulfonamides should be avoided in view of the bilirubin levels of the newborn. A short-term local treatment is acceptable, especially if the site is small.

2.6.8 Quinolones

Quinolones inhibit the bacterial enzymes topoisomerase II and IV that are important for the nucleic acid metabolism of bacteria. Quinolones

have a high affinity for cartilage and bone tissue which is highest in immature cartilage.

Pipemidic acid and *nalidixid acid* belong to the group of older quinolones. They have been displaced by the newer fluoroquinolones. The most important *fluoroquinolones* include *ciprofloxacin*, *enoxacin*, *levofloxacin*, *moxifloxacin*, *norfloxacin*, and *ofloxacin*. Several substances have been removed from the market because of severe side effects. *Garenoxacin*, *lomefloxacin*, *pefloxacin*, *rosoxacin*, and *sparfloxacin* are still available in some countries. *Gatifloxacin* and *nadifloxacin* are only used as local agent.

Quinolones cross the placenta and are found in the amniotic fluid at low concentrations.When moxifloxacin is used about 8% of the maternal serum concentration can be measured in the amniotic fluid, and with lovofloxacin about 16% (Ozyüncü 2010).

Quinolones have not been found to be teratogenic in animals but severe, irreversible damage to joint cartilages was noted in young dogs treated after birth with quinolones (e.g. Gough 1992). Such alterations have not been described in prenatally exposed children. Many publications failed to show indications of joint cartilage damage or an increased risk of malformations (Bar-Oz 2009, Cooper 2009, Larsen 2001, Loebstein 1998, Schaefer 1996, Berkovitch 1994). One study expressed concern that the prenatal use of fluoroquinolones may be associated with an increased risk of bone malformations (Wogelius 2005). Although not resembling each other, in three out of four birth defects the skeleton was affected. However, in this study of 130 women who redeemed a prescription for fluoroquinolones during the first trimester, or 30 days before conception, the total malformation rate was not increased (Wogelius 2005). In a prospective cohort study with 949 women who were exposed to a fluorquinolone during the first trimester, neither the rate of major birth defects, nor the risk of spontaneous abortion were increased compared to a control group (Padberg 2014). Altogether, most data are available for norfloxacin and ciprofloxacin and, to a lesser extent, for levofloxacin, moxifloxacin, ofloxacin and pefloxacin. There are few or no data for the other fluoroquinolones.

There have been no reports of undesirable side effects after topical use of quinolones during pregnancy.

Recommendation. Quinolones are antibiotics of second choice during pregnancy. In well-founded situations, when better studied antibiotics are ineffective, those quinolones that are well documented may be preferred such as norfloxacin or ciprofloxacin. A detailed ultrasound examination may be offered after exposure with the other fluoroquinolones during the first trimester. Local treatment with quinolones is acceptable throughout pregnancy.

2.6.9 Nitrofurans and drugs for urinary tract infections

Nitrofurantoin is a chemotherapeutic agent for drug-resistant urinary tract infections (UTIs) and for the prevention of recurrent UTIs. It acts as a bacteriostatic, but is also bactericidal at higher concentrations. Details of its mechanism of action remain to be clarified. After an oral dose, therapeutic effective levels are attained only in the urinary tract.

Several publications do not support an association between nitrofurantoin and congenital malformations (Nordeng 2013, Goldberg 2013,

Czeizel 2001d, Ben David 1995), although in a number of studies, some of them with methodological faults, weakly significant findings were noted for craniosysnostosis, ophthalmic malformations, oral clefts, and cardiovascular defects (Crider 2009, Källén 2005b, Källén 2003). A case-control study observed an increased risk of craniosynostosis after intrauterine exposure to nitrosatable drugs (Gardner 1998).

As nitrofurantoin lowers the activity of glutathione reductase, discussions arise periodically as to whether an intrauterine exposure could trigger a fetal hemolysis. Bruel (2000) reported a mature newborn with hemolytic anemia whose mother took nitrofurantoin during the last gestational month. Nitrofurantoin is often used during pregnancy, and fetal hemolysis has not been commonly observed; therefore, a relevant risk is not likely. However, Nordeng (2013) observed an increased risk of neonatal jaundice after maternal nitofurantoin treatment in the last 30 days before delivery.

There is a case report of a pregnant woman who developed a toxic hepatitis after having been exposed to nitrofurantoin in her thirty-sixth week (Aksamija 2009). In another case a woman took nitrofurantoin in her thirty-third week and was interpreted to present a gestational nitrofurantoin-induced pneumonia (Mohamed 2007).

The nitrofurantoin derivative *nifuroxazide* is used for the treatment of diarrhea. There are no documented reports of its tolerance in pregnancy nor evidence of effectiveness.

Nifurtimox is a nitrofuran used for treatment of Chagas disease. Experience for pregnancy is very limited and the World Health Organization recommends that nifurtimox should not be taken by pregnant women (WHO 2013a). One study about safety included 14 pregnant women, but did not give information about the pregnancy outcome (Schmid 2012).

For local treatment the nitrofurans *furazolidone*, *nitrofural*, and *nifuratel* are available. There has been no evidence of embryo- or fetotoxic risk in local applications. The use of local nitrofurans, especially as vaginal therapy, remains controversial and needs to be critically assessed not only during pregnancy.

Methenamine is a UTI medication that releases the antiseptic *formaldehyde* into the urine. *Methenamine mandelate* had been used for chronic UTIs due to *E. coli* and unproblematic germs. Effectiveness and tolerance of the agent remain controversial. Embryo- or fetotoxic problems have not been reported.

There are no reports about the use of the hydroxy-quinolone derivative *nitroxoline* in pregnancy.

▶ Fosfomycin

Fosfomycin is a broad-spectrum antibiotic that is bactericidal by inhibiting the synthesis of the bacterial cell wall. It is used as an intravenous injectable and as a reserve antibiotic in severe infections such as osteomyelitis. *Fosfomycin tromethamine* is an orally taken salt of fosfomycin used for the treatment of uncomplicated UTIs. Some authors also recommend the oral use during pregnancy (e.g. Falagas 2010, Bayrak 2007). These studies, however, are primarily focused on the effectiveness of fosfomycin tromethamine, not on the risk for the newborn. Overall, the experience argues against a teratogenic and fetotoxic potential in humans.

Recommendation. Nitrofurantoin can be given during pregnancy to treat urinary tract infections when the antibiotics of choice have been ineffective. If possible, it should be avoided towards the end of pregnancy. The use of nifuroxazide, nifurtimox, local nitrofurans, methenamine, and nitroxoline should be avoided during pregnancy.

When the antibiotics of choice in pregnancy cannot be used, fosfomycin tromethamine may be used to treat urinary tract infections in pregnancy. The intravenous application of fosfomycin should be restricted to severe bacterial infections with problematic germs.

2.6.10 Nitroimidazole antibiotics

Nitroimidazoles are effective bactericidal agents against anaerobes and protozoa. They are converted into metabolites that impede intracellular bacterial DNA synthesis. The main representative of the nitroimidazoles is *metronidazole*. Metronidazole is now being recommended by some investigators for the treatment of bacterial vaginosis in pregnancies at high risk for preterm delivery, as a strategy to decrease this risk (review by Joesoef 1999). Others, however, failed to notice an improvement in the incidence of prematurity (Shennan 2006, Andrews 2003, Klebanoff 2001).

After oral and intravenous administration, concentrations as high as those in the mother are reached in the embryo/fetus. Significant systemic absorption occurs after vaginal application, exposing the fetus as well. The pharmacokinetic profile of metronidazole did not change at the different time points assessed during pregnancy, and did not differ from nonpregnant patients (Wang 2011).

Like all nitroimidazoles, metronidazole displays an experimentally mutagenic and cancerogenic potential (review by Dobias 1994) that has not been confirmed in humans. An investigation that ranged over 20 years did not show any indication of an increased risk of cancer when metronidazole was used (Beard 1988).

On the basis of over 3,000 analyzed pregnancies, it can be stated that metronidazole has no teratogenic potential in humans (e.g. Koss 2012, Diav-Citrin 2001, Czeizel 1998). Suggestions from the Hungarian Malformation Registry of a link between vaginal therapy with metronidazole and miconazole during the second and third month, and an increased appearance of syndactylies and hexadactylies have not been confirmed by other investigators (Kazy 2005a).

Nimorazole and *tinidazole*, both registered for the treatment of trichomonas infections, amebiasis, and bacterial vaginosis, cannot be evaluated sufficiently because of the lack of human data – the same applies to *ornidazole*. So far, there are no reports of human teratogenicity.

Recommendation. Metronidazol may be used in pregnancy when indicated. A single oral dose of 2 g is preferable to vaginal administration spread over several days, particularly as there are doubts about the effectiveness of the vaginal application. A parenteral administration is only indicated for a serious anaerobic infection. Metronidazole is to be preferred to the less examined nitroimidazoles.

2.6.11 Aminoglycosides

The aminoglycoside antibiotics *amikacin*, *framycetin*, *gentamicin*, *kanamycin*, *neomycin*, *netilmicin*, *paromomycin*, *ribostamycin*, *streptomycin*,

and *tobramycin* inhibit protein synthesis and are bactericidal primarily for Gram-negative germs. After oral administration only a minimal portion of aminoglycosides is resorbed. After parenteral administration of about 20–40% of the maternal plasma concentration is detectable in the fetus. *Spectinomycin* is an aminocyclitol antibiotic closely related to the aminoglycosides.

Oto- and nephrotoxic side effects are also known to occur in nonpregnant patients when aminolgycosides are used parenterally. There are case reports about the parenteral use of kanamycin and streptomycin during pregnancy describing auditory problems, even deafness, in children exposed *in utero* (e.g. Jones 1973, Conway 1965, Robinson 1964). A similar case was reported in connection with gentamicin (Sánchez Sainz-Trápaga 1998). An investigation of the hearing ability of 39 children whose mothers had received gentamicin intravenously during pregnancy found no deficiencies. This argues against a major ototoxic risk of gentamicin when used in pregnancy (Kirkwood 2007).

Theoretically, a fetal nephrotoxic risk exists because aminoglycosides concentrate in the fetal kidneys. A case report about a connatal kidney dysplasia after maternal gentamicin therapy (Hulton 1995) does not prove a clinically relevant human risk, nor does a case of a hydronephrosis and suspected stenosis at the uteropelvic junction with lethal outcome, where the mother had been treated for UTI first with *ciprofloxacin* and then with gentamicin at weeks 4–5 (Yaris 2004).

Except for these case reports, studies argue against a high oto- or nephrotoxic risk of gentamicin in the fetus and newborn. There has been no increase in the observation of malformations (Czeizel 2000e). No untoward effects have been described with aminoglycosides as local treatment during pregnancy.

Experience with *spectinomycin* is insufficient to analyze a risk in pregnancy.

Recommendation. Aminoglycosides should only be used parenterally in life-threatening infections with difficult Gram-negative pathogens and when first-choice antibiotics fail. The serum levels need to be monitored regularly during the treatment. A risk-based termination of pregnancy or invasive diagnostic are not required (Chapter 1.15). If the parenteral therapy had been extensive, renal function should be monitored in the neonate and an auditory test should be performed. If local or oral application of aminoglycosides is indicated, they can be given because systemic absorption is minimal by these routes.

2.6.12 Glycopeptide and polypeptide antibiotics

Glycopeptide antibiotics

The glycopeptides *vancomycin* and *teicoplanin* are bactericidal only for Gram-positive pathogens by inhibiting their cell wall synthesis. They are considered reserve antibiotics to be used against MSRA and multiresistant enterococci. To avoid the development of resistance, their application should be critically appraised, and possibly limited only to fighting problematic pathogens. Oral glycopeptides are hardly resorbed. This is useful when treating pseudomembranous enterocolitis with vancomycin. However, in this situation metronidazole (Section 2.6.10) should be considered as an alternative, as vancomycin therapy is more expensive, and to prevent the selection for vancomycin-resistant enterococci.

Vancomycin crosses the placenta reaching the fetus in relevant quantities (Laiprasert 2007). It has not shown teratogenic effects in animal studies. Experience with treatment in human pregnancy is limited to a

few case reports. There were no observations of malformations, kidney damage, or hearing deficits (Reyes 1989).

Experience with teicoplanin and the new lipoglycopeptides *dalbavancin*, *oritavancin* and *telavancin* is insufficient to analyze a risk in pregnancy. *In vitro* telavancin crosses the human placenta, with fetal concentrations reaching less than 3% of maternal concentrations (Nanovskaya 2012).

Recommendation. Glycopeptides should only be used in cases of life-threatening bacterial infections; vancomycin should then be preferred.

Lipopeptide antibiotics

Daptomycin belongs to a new class of cyclic lipopeptides and is effective exclusively against Gram-positive bacteria. It works by interfering with the bacterial cell membrane and protein synthesis, and is indicated to treat complicated infections with difficult pathogens. In animal experiments, daptomycin crossed the placenta and was not teratogenic. Two children whose mothers took daptomycin in the fourteenth and twenty-seventh weeks were unremarkable (Stroup 2010, Shea 2008).

Recommendation. The use of daptomycin is limited to cases of life-threatening bacterial infections.

Polypeptide antibiotics

Polymyxins belong to the polypeptide antibiotics that are bactericidal by interfering with the transport mechanism of the cell wall. While the polymyxin *colistin* is today mostly used locally, it can also be applied parenterally where there is an infection with multi-resistant Gram-negative germs. In patients with mucoviscidosis it is used as an inhalative. Enterally colistin is not resorbed; therefore its oral administration is used to selectively decontaminate the intestinal tract.

The polypeptide antibiotics *bacitracin*, *polymyxin B*, and *tyrothricin* are used locally. Only limited experience is available in the application of polypeptide antibiotics during pregnancy and do not indicate a substantial risk (Kazy 2005b).

Recommendation. The parental use of colistin is limited to cases of life-threatening bacterial infections. The local and oral application of polypeptide antibiotics need to be critically assessed.

2.6.13 Other antibiotics

Chloramphenicol

Chloramphenicol and *Tiamphenicol* inhibit bacterial protein synthesis and have bacteriostatic activity. Chloramphenicol is relatively toxic, and can cause severe agranulocytosis. It crosses the placenta well and can reach therapeutic concentrations in the fetus. In premature and term births it may lead to the grey baby syndrome. Chloramphenicol can reach toxic levels in the neonate even when only the mother has been treated. There have been no suggestions of malformations (Czeizel 2000f).

Experience with thiamphenicol is insufficient to analyze a risk in pregnancy.

Recommendation. The systemic use of chloramphenicol and thiamphenicol is contraindicated throughout pregnancy. Exceptions are life-threatening maternal infections that do not respond to less toxic antibiotics. When systemic treatment is absolutely necessary before birth, it is important to observe the newborn for toxic symptoms. A local application is also to be avoided during pregnancy.

Dapsone

Dapsone, used among other indications against leprosis, apparently has no teratogenic potential (e.g. Lush 2000, Bhargava 1996). However, cases of hemolytic anemia have been reported in mothers and newborns. As dapsone bears a structural similarity to the sulfonamides, it has been argued that it might compete with bilirubin for protein binding, and thus could lead to hyperbilirubinemia in the newborn.

Recommendation. During pregnancy, dapsone should be reserved for specific indications. If treatment took place in the first trimester, a detailed ultrasound examination should be offered to ascertain the normal development of the fetus.

Fidaxomicin

Fidaxomicin is a macrocyclic antibiotic which is approved for the treatment of infections with Clostridium difficile. Enterally fidaxomicin is very poorly resorbed. No experiences have been reported about its use during pregnancy.

Recommendation. Fidaxomicin should be avoided in pregnancy. If treatment took place in the first trimester, a detailed ultrasound examination should be offered to ascertain the normal development of the fetus.

Linezolid

Linezolid is a member of the oxazolidinone class, a new group of antibiotics. It acts bactericidally by inhibiting bacterial protein synthesis and is indicated in the treatment of multi-resistant pathogens. There is just one case report about the use of linezolid during pregnancy. After intrauterine exposure from gestational weeks 14 to 18 a healthy infant was delivered at term (Mercieri 2010).

Recommendation. With the lack of experience, linezolid should only be used for severe infections with problematic germs. If treatment took place in the first trimester, a detailed ultrasound examination should be offered to ascertain the normal development of the fetus.

Pentamidine

The antiprotozoal agent *pentamidine*, among others effective in Pneumocystis pneumonia, has not been evaluated sufficiently in pregnancy to

estimate its embryotoxic potential for humans. Usually it can be replaced by other antibiotics, e.g. *co-trimoxazole* (Section 2.6.7).

Recommendation. Pentamidine is to be reserved in pregnancy for special situations when better tested antibiotics are not effective. If treatment took place in the first trimester, a detailed ultrasound examination should be offered to ascertain the normal development of the fetus.

Rifaximin

Rifaximin is an antibiotic to treat travelers' diarrhea. There is not enough experience regarding its use in pregnancy. Minimal enteral resorption and negative animal testing suggest that a high embryotoxic risk is unlikely.

Recommendation. If possible, rifaximin should be avoided during pregnancy.

Streptogramins

Streptogramins are a group of cyclic peptide antibiotics that inhibit, like *macrolides* and *lincosamides*, the synthesis of bacterial proteins. They are derivatives of the naturally occurring *pristinamycin*. The later developed derivatives *quinupristin* and *dalfopristin* are used in a fixed combination. Streptogramins should only be applied as reserve antibiotics for infections with highly resistant Gram-positive germs. Reports about use in pregnancy have not been available.

Recommendation. Streptogramins are to be avoided during pregnancy. If treatment took place in the first trimester, a detailed ultrasound examination should be offered to ascertain the normal development of the fetus.

2.6.14 Tuberculosis and pregnancy

Active tuberculosis (TB) requires treatment in pregnancy, as the disease endangers not only the mother, but also the fetus. Pregnancy does not seem to affect the course of TB. The prevalence of congenital TB is less than 1% where no treatment is initiated. Lin (2010) investigated 761 newborns of mothers who had received treatment for TB during the gestation. Their children were smaller and had lower birth weights than the control group of children of healthy mothers.

There are slight differences in the recommendations of the different organizations in the world, such as the WHO (2010a), the International Union against Tuberculosis and Lung Disease (IUATLD), and several national organizations (e.g. Blumberg 2003). Treatment considerations depend on disease status and drug resistance. First-line drugs for the treatment of TB during pregnancy are *isoniazid* (+*pyridoxine*), *rifampicin*, *ethambutol* and *pyrazinamide*. These standard medications have not shown teratogenic or fetotoxic effects in humans (e.g. Bothamley 2001). As far as we know today, TB drugs reach the fetus in relevant quantities. An increasing development of resistance makes it harder to choose the right medication in pregnancy. Pregnant women with multidrug-resistant TB (MDR-TB) may also require second-line antituberculous

drugs; the necessity for treatment should be weighed against the risk for the fetus on an individual base. Current experiences in the management of MDR-TB argue against a high risk of the reserve drugs for the newborn (Drobac 2005, Shin 2003). Streptomycin, however, should be avoided because of its ototoxic potential.

Ethambutol

Ethambutol is a bacteriostatic drug used against tuberculosis. It can cross the placenta, but the risk of congenital malformations when used during pregnancy appears to be low. There are no reports indicating that ethambutol can cause ocular toxicity in the fetus, as it does in adults, when given in higher doses.

Recommendation. Ethambutol is a first-line drug for treatment of tuberculosis during pregnancy.

Isoniazid

Isoniazid (INH) has proven to be a highly effective drug against many strains of mycobacterium, and can be used for tuberculous prophylaxis and for treatment of an active disease during pregnancy. Although INH can cross the placenta, it does not appear to be teratogenic, even when given during the first trimester. The older literature contains case reports of different malformations and neurological damages in prenatally exposed children. INH intake, lack of pyridoxine, co-medication, and even the TB disease itself was blamed. Newer publications did not confirm a teratogenic risk (e.g. Taylor 2013, Czeizel 2001e). In summary, experiences speak against a major risk. INH increases pyridoxine metabolism, which may be responsible for CNS toxicity. To prevent a possible vitamin B6 deficiency, INH should be given during pregnancy in combination with *pyridoxine*.

Recommendation. Isoniazid is a first-line drug for treatment of tuberculosis during pregnancy. It needs to be given together with pyridoxine.

Pyrazinamide

Pyrazinamide (PZA) is an antibiotic with specific effectiveness against Mycobacterium tuberculosis. As its structure resembles nicotinamide, it is assumed that it intervenes with the nucleic acid metabolism of the bacterial cell. PZA has effective bactericidal properties. Systematic studies of its tolerance in pregnancy are lacking. So far, there has been no evidence of embryo- or fetotoxic effects in humans. The use of PZA during pregnancy is recommended in several guidelines (e.g. WHO 2010a). The American Thoracic Society recommends in its guidelines to hold PZA as a reserve drug during pregnancy, as there are currently insufficient data about its teratogenicity (Blumberg 2003). If PZA is not used, treatment may be prolonged.

Recommendation. Pyrazinamide may be used during pregnancy to treat active TB.

Rifampicin

Rifampicin also called *rifampin*, inhibits bacterial RNA polymerase and is effective as a bactericidal agent against different pathogens, particularly mycobacteria. Rifampicin can cross the placenta. In animal experiments, teratogenic effects were seen with doses 5–10 times higher than in human treatment. Because rifampicin inhibits DNA-dependent RNA polymerase, there has been concern that it might interfere with fetal development. Until now, no reports in the literature have confirmed this fear. There is apparently no increased risk of malformations. A long-term therapy of the mother could result in inhibition of vitamin K synthesis, and result in a higher bleeding tendency in neonates.

Recommendation. Rifampicin is a first-line drug for treatment of tuberculosis during pregnancy. When used near term the newborn should receive an extended vitamin K prophylaxis (Chapter 2.9). Regarding other infections such as MRSA, rifampicin should only be administered when the drugs of first choice for pregnancy cannot be used.

Streptomycin

Streptomycin is an aminoglycoside that is used parenterally in the treatment of TB. It is bactericidal, particularly affecting germs that proliferate extracellularly. Its ototoxicity can also hurt the fetus (Section 2.6.11).

Recommendation. Streptomycin is contraindicated during pregnancy because of its ototoxic properties. Inadvertent exposure does not require risk-based termination of pregnancy or invasive diagnostic procedures, but hearing tests should be performed after birth (Chapter 1.15).

Other tuberculostatics

Aside from the above discussed first-line drugs for TB, reserve medications are available and used in cases of resistance or intolerance.

No systematic studies exist on the tolerance of *4-aminosalicylic acid (p-aminosalicylic acid*; PAS). So far, no evidence for embryo- or fetotoxic effects has been found in humans (e.g. Lowe 1964). *Capreomycin*, *ethionamide*, *protionamide*, *rifabutin*, *rifapentine*, *thioacetazone*, and *terizidone*, a prodrug of *cycloserine*, are all second-line agents used internationally for MDR-TB. The extent of documented experiences in pregnancy is limited, and insufficient for a differentiated risk assessment. Single case reports argue against a high teratogenic risk of these drugs (e.g. Lessnau 2003, Drobac 2005).

For additional reserve drugs for multi-resistant TB such as *amikacin*, see Section 2.6.11, and diverse quinolones, see Section 2.6.8; for other anti-infective agents, view the relevant sections of this chapter.

Recommendation. The reserve drugs discussed here should only be used for multi-resistant tuberculosis when standard therapy is not indicated. An inadvertent exposure during pregnancy does not require a risk-based termination or invasive diagnostic, but a detailed ultrasound examination should be carried out (Chapter 1.15).

2.6.15 Local antibiotics

Generally, each external antibiotic treatment needs to be examined carefully to see whether or not the bacterial infection is more effectively treated with systemic medication. The potential of local treatment is often overestimated. Further, with topical therapy, sensitization and resistance development need to be considered.

Fusafungine has bacteriostatic and anti-inflammatory effects and is used as a spray for the treatment of infections of the nose and throat area. There is insufficient experience about its application in pregnancy.

Fusidic acid is an antibiotic that is almost exclusively used externally; its prenatal tolerance has not been examined systematically, although the medication has been available for a long time. It has a narrow spectrum of effectiveness against Gram-positive bacteria (staphylococci) and is not recommended for an untargeted treatment.

Mupirocin is primarily bacteriostatic, affecting staphylococci and streptococci by inhibiting bacterial protein synthesis. It is especially used as a nasal ointment to eliminate MRSA. Mupirocin has not been examined systematically, but there is no evidence of undesirable effects in pregnancy.

Retapamulin is the first representative of the pleuromutilins that is approved for human treatment. It is applied as an ointment for short-term treatment of superficial skin infections. Retapamulin inhibits bacterial protein synthesis and is bacteriostatic, primarily for Gram-positive germs. Systemic resorption is minimal with topical use, but nevertheless, as experience in pregnancy has been limited, its application needs to be critically examined.

Taurolidine is an antimicrobial solution that can be used for lavage in peritonitis and for the prevention of infections with catheters. As a bactericidal agent, its mechanism of action is only partially clarified. There are no reported experiences in pregnancy.

See the corresponding sections for the local application of *aminoglycosides* (Section 2.6.11), *chloramphenicol* (Section 2.6.13), *quinolones* (Section 2.6.8), *macrolides* (Section 2.6.4), *nitrofurans* (Section 2.6.9), *nitroimidazoles* (Section 2.6.10), *polypeptide* antibiotics (Section 2.6.12), *sulfonamides* (Section 2.6.7), and *tetracyclines* (Section 2.6.6).

Recommendation. Externally used antibiotics are not suspected to be teratogenic. Nevertheless, the application of local antibiotics needs to be critically assessed. Antibiotics that are safe when used systemically may also be used locally. If another local antibiotic is absolutely necessary, it may be used in pregnancy.

2.6.16 Malaria prophylaxis and treatment in pregnancy

Apart from pregnant women living in malaria areas, pregnant women are increasingly traveling to tropical countries and need a suitable malaria prophylaxis. Increased resistance of malaria pathogens make it more difficult to suggest a general recommendation. The guidelines of tropical medicine

should be followed, also in pregnancy, according to the travel destination. Especially difficult is the management of malaria tropica caused by *Plasmodium falciparum*. Pregnancy enhances the clinical severity of falciparum malaria, especially in the primiparous and non-immune woman. Pregnancy alters a woman's immunity to malaria, making her more susceptible to malaria infection and increasing the risk of illness, severe anaemia, and death. Maternal malaria increases the risk of spontaneous abortion, stillbirth, prematurity, and low birth weight, and thus results in excess infant mortality (e.g. Bardaji 2011, Shulman 2003). Therefore, mosquito-bite prevention, prophylaxis, and treatment of malaria should not be shortened or omitted in an ongoing pregnancy. Traveling to areas with multidrug-resistant malaria should be avoided if possible.

The choice of drug for malaria prophylaxis and treatment during pregnancy depends on the local pattern of antimalarial drug resistance, the severity of the malaria, and the degree of pre-existing immunity. It is important to be well informed about the current recommendations for prophylaxis and treatment of malaria in the area to be visited. For travelers to malaria-endemic areas, a general recommendation is difficult because of increasing resistances. Depending on the drug, the chemoprophylaxis must be continued for up to 4 weeks after leaving the malarial region.

For women living in falciparum-endemic areas with stable transmission, the World Health Organization recommends the use of insecticide-treated nets (ITNs) and *intermittent preventive treatment* (IPT) with sulfadoxine-pyrimethamine during pregnancy (WHO 2013b, Nyunt 2010). IPT reduces maternal malaria episodes, maternal anaemia, placental parasitaemia, low birth weight, and neonatal mortality (review by McClure 2013). A prompt diagnosis and effective treatment of malaria infections is vital.

Although data from prospective studies are limited *quinine*, *chloroquine*, *proguanil*, and *clindamycin* (Section 2.6.5) are considered safe during early pregnancy. Pregnant women in the first trimester with uncomplicated malaria tropica should be treated with quinine plus clindamycin (if available) (WHO 2010b). For the second and third trimester the World Health Organization recommends *artemisinin* derivatives. The choice of combination partner is difficult because of limited information.

Reserve medications include the following: *amodiaquine*, *atovaquone*, *dapsone* (Section 2.6.13), *lumefantrine*, *mefloquine*, *piperaquine*, and *pyrimethamine* plus *sulfadoxine*. *Doxycycline* is contraindicated after the sixteenth gestational week (Section 2.6.6). *Halofantrine* and *primaquine* should be avoided. See the relevant sections of this chapter about the specific active substrates.

During gestation plasma concentrations of many antimalaria agents are lower and their elimination is enhanced. This can result in treatment failure. Thus, in each patient dose and dose interval need to be assessed individually.

Recommendation. Generally, the physician should discuss with a patient if the trip to a tropical region could be postponed (Section 2.6.36). The risk of exposure can be reduced by long clothes, mosquito netting, and repellents. In no case should medications be denied for prophylaxis or treatment on behalf of a pregnancy, as the potential risk for the unborn child predominates. If medications with inadequate pregnancy experience are used in the first trimester, a detailed ultrasound examination should be offered. A risk-based termination is not justified when the above-described medications have been used in pregnancy (Chapter 1.15).

Amodiaquine

Amodiaquine, like *chloroquine*, belongs to the group of 4-aminoquinolines. It can cause severe side effects such as liver damage and agranulocytosis, and for this reason, is unsuitable for prophylaxis. Its use is limited as a reserve medication for malaria. There has been no evidence of tetatogenicity (review by Thomas 2004), but experiences are limited. With regard to early pregnancy, only single case reports have been published. One study found only mild maternal side effects in 450 pregnant women who had been treated in the second or third trimester. An increase in miscarriages, prematurity, stillbirth, or malformations was not observed (Tagbor 2006).

Recommendation. Amodiaquine may be used as a reserve medication for the treatment of malaria.

Artemisinin derivatives

Artemisinin and its derivatives *artemether*, *artemotil*, *artesunate*, and *dihydroartemisinin*, are increasingly used against malaria as *Plasmodium falciparum* has developed resistance to other drugs. These compounds combine rapid blood schizonticide activity with a wide therapeutic index. Artemisinins should be given as combination therapy to protect them from resistance. Typical combinations of such *artemisinin-based combination therapy* (ACT) are artemether plus *lumefantrine*, artesunate plus *amodiaquine*, artesunate plus *mefloquine*, artesunate plus *sulfadoxine-pyrimethamine*, and dihydroartemisinin plus *piperaquine*

First trimester experiences with the use of artemisinin derivatives are limited. A number of studies contain data of more than 250 pregnant women treated with an artemisinin derivative during the first trimester, without showing evidence of a teratogenic risk (Mosha 2014, Adam 2009, Clark 2009, WHO 2006). Manyando (2010) more commonly found umbilical hernias in an additional 140 children whose mothers had been treated with artemether and lumefantrine. After 12 months most of these hernias were not detectable anymore.

There are experiences with more than 1,500 pregnant women who used artemisinin derivatives in the second and third trimester (e.g. Piola 2010, Bounyasong 2001, Deen 2001, McGready 2001, Phillips-Howard 1996). In summary, these studies did not find an increased risk in miscarriages, stillbirths, and malformations. To some degree the artemisisin derivatives were better tolerated by pregnant women, and were more effective than treatments of the control group. As plasma levels of artemether are decreased during pregnancy, it has been suggested that the dose and the dose interval may have to be adjusted (e.g. Tarning 2013, Morris 2011).

These reassuring data led the WHO (2010b) to recommend using artemisinin derivatives as medications of choice for malaria tropica in the second and third trimester. It does not specify what combination is recommended in the context of ACT. During the first trimester, based on a lack of experiences, the WHO views artemisinin derivatives as reserve medications that should not be withheld in an individual case where needed.

Recommendation. Artemisinin derivatives may be used in the second and third trimester. In the first trimester they are reserve medications for the treatment of malaria.

Atovaquone

Atovaquone is a broad-spectrum anti-protozoal drug that is also used in Pneumocystis pneumonia. Monotherapy quickly leads to resistance, thus it is combined with *proguanil* when used for malaria prophylaxis and treatment.

Experience with atovaquone is limited in pregnancy. A Danish cohort study based on a prescription register with 149 women exposed during their first trimester to atovaquone, 93 of them exposed at any time in weeks 3 through 8 after conception, found no increased risk for birth defects (Pasternak 2011). When used in the second and third trimester, small studies observed no adverse effects (McGready 2005, Na-Bangchang 2005). Available data are insufficient for a differentiated risk assessment, but do not suggest a teratogenic risk. McGready (2003) discusses the need of a dose adjustment as clearance increases and levels decrease during pregnancy.

Recommendation. Atovaquone may be used as a reserve medication for the treatment of malaria.

Chloroquine

Chloroquine, an antimalaria drug of the group of 4-aminoquinolines, works well and effectively as a schizonticidal drug against the erythrocytic forms of all types of plasmodia. Today though, almost all pathogens of the potentially lethal malaria tropica have become resistant to this rather well tolerated, and for many decades, useful medication. Resistance has also been noted for *Plasmodium vivax*, the pathogen of the less severe malaria tertiana. *Plasmodium ovale* and *plasmodium malariae* still remain mainly sensitive to chloroquine.

Chloroquine is not embryo- and fetotoxic when used at the usual dose for malaria prophylaxis or for a three-day treatment of a typical malaria attack (McGready 2002, Phillips-Howard 1996). Current evidence does not suggest fetal ocular toxicity when chloroquine was used as antimalarian medication during pregnancy (review by Osadchy 2011). Lee (2008) examined 12 pregnant women and nonpregnant controls, and did not find any changes in the pharmacokinetics or the serum level of chloroquine.

The anti-inflammatory properties of chloroquine are used also for antirheumatic therapy (Section 2.12.8). Antirheumatic doses of chloroquine are higher than those used for malaria prevention.

Recommendation. Chloroquine may be used throughout pregnancy for the prophylaxis and treatment of malaria. If chloroquine resistance of the parasite is likely or has been demonstrated, other drugs must be used.

Halofantrine

Halofantrine has a rapid schizonticidal effect upon the erythrocytic forms of those plasmodia that are resistant to chloroquine and other antimalarials. Halofantrine prolongs the QT interval in the EKG. Becauses it can provoke life-threatening cardiac arrhythmias in patients with heart disease, or in conjunction with other arrhythmogenic medications, halofantrine is no longer recommended. The limited experiences in pregnancy allow no differentiated risk analysis.

Recommendation. Halofantrine is only to be used in cases of acutely threatening malaria that cannot be managed with better tested and less toxic drugs. When cardiac problems are an issue, other antimalaria medications must be used.

Lumefantrine

Lumefantrine belongs to the group of arylamine alcohols like quinine, mefloquine, and halofantrine. *Artemether* plus lumefantrine is currently a popular artemisinin-based combination therapy. Few experiences are available regarding its application in the first trimester without showing evidence of a teratogenic risk (e.g. Mosha 2014). For the second and third trimester, studies with several hundred patients have been reported and do not indicate a major risk (Piola 2010, McGready 2008). Manyando (2010) found only a mild increase in umbilical hernias in 140 children whose mothers took artemether and lumefantrine during the first trimester. Most of these had disappeared when follow-up examination was conducted 12 months later. In summary, current experiences do not suggest a major embryo- or fetotoxic risk of lumefantrine. During pregnancy, the plasma concentration is lower and the elimination enhanced, thus increasing the risk of treatment failure (e.g. Tarning 2009, McGready 2008).

Recommendation. Lumefantrine may be used as a reserve medication for the treatment of malaria.

Mefloquine

Mefloquine displays an effective and rapid activity against the erythrocytic forms of all plasmodia. Current experiences with more than 2,000 treated pregnant women, several hundred of them in the first trimester, do not suggest a teratogenic or fetotoxic potential in humans (e.g. Schlagenhauf 2012, Bounyasong 2001, McGready 2000).

One single study of the use of mefloquine has been debated as finding an increased rate of stillbirths. This study compared 200 pregnant women who received mefloquine for malaria, and found them to have a significantly higher rate of stillbirth than those who had been treated with quinine and other antimalarials (Nosten 1999). Other studies, however, have not confirmed this risk, and mefloquine has been an established medication in pregnancy for some time.

Recommendation. Mefloquine may be used throughout pregnancy for the prophylaxis and treatment of malaria if there is no resistance.

Piperaquine

A fixed oral combination of the bisquinolone *piperaquine* and *dihydroartemisinin* (DHP) is a new and promising artemisinin-based combination therapy. The mechanism of action of piperaquine is unknown. An Indonesian observational study detected a higher rate of abortion after first trimester exposure to dihydroartemisinin-piperaquine (Poespoprodjo 2014). This observation was based on five abortions among eight pregnancies (63%). The same study found a lower risk of perinatal mortality after dihydroartemisinin-piperaquine in the second and third trimester compared to quinine-based regimens. The limited experiences in pregnancy allow no differentiated risk analysis. No significant pharmacokinetic differences between pregnant and nonpregnant women were reported in two small studies (Adam 2012, Hoglund 2012).

Recommendation. Piperaquine may be used as a reserve medication for the treatment of malaria.

Primaquine

Primaquine, an 8-aminoquinoline derivative, is effective against the intrahepatic permanent forms of *Plasmodium vivax* and *Plasmodium ovale*. It is used for the complete elimination of pathogens in combination with a blood schizontocide for the erythrocytic parasites. Primaquine should not be used in pregnancy because of the potential risk of hemolytic effects in the fetus. As yet, there are no studies that permit a well-grounded risk assessment. However, there is no substantial evidence for a teratogenic potential in humans (Phillips-Howard 1996).

Recommendation. Primaquine is not a therapeutic option during pregnancy. A prophylactic elimination of hepatic spores should usually be postponed for a time after birth.

Proguanil

Proguanil, an older medication for malaria prophylaxis belonging to the folic acid antagonists, is experiencing a renaissance as it has become useful in the face of increasing chloroquine resistance. Most often it is applied in combination with the synergistic *atovaquone*. There is no evidence of an embryotoxic potential in humans (e.g. Pasternak 2011, McGready 2005). McGready (2003) discuss the need to adjust the dose as clearance is increased and blood levels decreased during pregnancy.

Recommendation. Proguanil may be used throughout pregnancy for prophylaxis and treatment of malaria provided there is no resistance.

Pyrimethamine/sulfadoxine

Pyrimethamine is an inhibitor of folic acid synthesis that is also used in the treatment of toxoplasmosis and Pneumocystis pneumonia. In malaria

treatment it is only applied in combination with another folic acid antagonist such as *sulfadoxine* (Section 2.6.7). This particular combination is used for *intermittent preventive treatment* (IPT) during pregnancy. However, increasing resistance has started to limit the effectiveness of this popular combination (Newman 2003).

As animal experiments indicated embryotoxic effects, concerns had been raised about the use of these folic acid antagonists in early pregnancy. Numerous investigations, however, have not demonstrated an increased malformation risk in humans (e.g. Manyando 2010, Phillips-Howard 1996).

Some studies suggest that pregnancy adversely alters the pharmacokinetics of pyrimethamine and sulfadoxine (e.g. Karunajeewa 2009, Green 2007). As data are inconsistent, a general recommendation about dose adjustments in pregnancy is difficult. When sulfadoxine-pyrimethamine is given in early pregnancy, it should be supplemented by folic acid until the tenth week. The WHO recommends 0.4–0.5 mg per day, as a co-administration of high dose (5 mg daily) compromises the efficacy of sulfadoxine-pyrimethamine in pregnancy (WHO 2010b).

Recommendation. Pyrimethamine in combination with sulfadoxine may be administered for the treatment of malaria. For toxoplasmosis it is the drug of choice when combined with a long-term sulfonamide, especially after the first trimester. When pyrimethamine is given in early pregnancy, it should be supplemented with folic acid, see also Chapter 2.18.8.

Quinine

Quinine is the oldest antimalarial agent. It works well and effectively as a schizonticidal drug against the erythrocytic forms of all Plasmodium species. Despite a relatively high toxicity and a narrow therapeutic range, it is used again increasingly in the treatment of chloroquine-resistant malaria. In combination with clindamycin (Section 2.6.5) its effectiveness is increased. Concentrations in the fetus are just as high as in the mother, and are potentially toxic.

In some case reports it was observed that children had auditory or visual defects after the use of quinine in pregnancy. However, in those cases considerably higher doses had been administered than currently in use. There is no evidence of an increased risk of abortion or preterm delivery with the use of a standard dosage of quinine for treatment of acute malaria (Phillips-Howard 1996). These findings were confirmed by other studies with several hundred pregnant women exposed during the first trimester, where no increased rates of spontaneous abortion, congenital malformations, stillbirth or low birth weight were found (e.g. Adam 2004b, McGready 2002).

Quinine increases the secretion of insulin (Elbadawi 2011). Especially in the last part of pregnancy, severe maternal hypoglycaemia has been induced by quinine therapy. Due to the risk of hypoglycemia, the WHO (2010b) guidelines prefer to use an artemisinin combination for the management of malaria tropica from the second trimester on. A study of the metabolism of quinine in pregnant and nonpregnant women failed to show significant pharmacokinetic differences. The authors concluded that dose adjustment is not necessary during pregnancy (Abdelrahim 2007). Induction of contractions with high doses of quinine cannot be excluded.

Quinine is a component of some analgesic compounds and of certain beverages, although in lower and apparently nonembryotoxic doses.

Recommendation. Despite its toxicity, quinine belongs to the drugs of choice when dealing with chloroquine-resistant malaria tropica in pregnancy. In this situation the potential risk of treatment is much smaller for the fetus than the danger of a severe maternal disease. Attention needs to be paid to possible maternal hypoglycemia. Even though embryotoxic effects due to quinine in analgesic compounds are not to be expected, these agents should be avoided because they do not conform to good therapeutical practice. The same holds for the regular or excessive consumption of quinine drinks.

2.6.17 Azole antifungals

Azole antifungals for systemic use

Azole derivatives inhibit the ergosterol biosynthesis, thereby causing disturbances in the permeability and functions of the fungal cell membrane. Azole antifungals include two broad classes, imidazoles and triazoles. In animal experiments azole antifungals cross the placenta and are teratogenic at high doses.

With regard to the use of the triazole derivative *fluconazole* in pregnancy, there was a report of three children (two of them siblings) with craniofacial, skeletal, and cardiac malformations, similar to those seen in animal studies (Pursley 1996). Because of meningitis, their mother had used high doses of fluconazole (400–800 mg daily) through or beyond the first trimester on a long-term basis. Additional case reports have described two births involving craniofacial, limb, and cardiac defects in two mothers who used fluconazole (Lopez-Rangel 2005, Aleck 1997). Those cases shared some characteristics with the Antley–Bixler syndrome.

However, there was no evidence of an increased risk of malformation in a prospective cohort study with 226 women exposed during the first trimester (Mastroiacovo 1996). In several other studies, first trimester exposure to low-dosage regimens of fluconazole for vaginal candidiasis did not appear to cause an increased risk of malformations (e.g. Jick 1999, Campomori 1997, Inman 1994).

Danish cohort studies based on a prescription register also could not find an increased risk of birth defects after first trimester exposure in several thousand pregnant women (Nørgaard 2008, Sørensen 1999). An extended analysis of the Danish data observed an increased risk for tetralogy of Fallot based on seven cases (prevalence 0.1%) compared to unexposed pregnancies (OR 3.16; 95% CI 1.49–6.71). The rate of major birth defects was not increased (Mølgaard-Nielsen 2013). In most cases the low and single dose consisted of 150 mg fluconazole usually used for a vaginal yeast infection.

Itraconazole is a triazole derivative with wide-spectrum activity. There has been no evidence of teratogenicity in prospective studies examining several hundred women with first trimester exposure (e.g. de Santis 2009, Bar-Oz 2000); most of the exposures were short-term. A Danish register analysis did not find an increased risk of birth defects among 687 women with a first trimester prescription of itraconazole (Mølgaard-Nielsen 2013).

The imidazole derivative *ketoconazole* is usually avoided in systemic use because it is poorly tolerated and has many suitable alternatives. Ketoconazole is administered on occasion for the treatment of Cushing syndrome as it inhibits steroid synthesis. Theoretically, by decreasing testosterone synthesis, it might impede the sexual development of male foetuses; however, this has not been described. Ketoconazole has been used in several cases in pregnancy with good maternal and fetal outcome (e.g. Boronat 2011, Berwaerts 1999, Amado 1990). A retrospective study from data of the Hungarian Malformation Registry based on 18 exposed subjects shows no evidence of an increased risk of malformations after systemic use of ketoconazole (Kazy 2005c). An analysis of a Danish register did not observe a significantly increased risk of birth defects among 72 pregnant women with a prescription for this agent during first trimester (Mølgaard-Nielsen 2013).

For *posaconazole* and *voriconazole* which are used for aspergillosis and other invasive mycoses, information is lacking about use during pregnancy. There is only one published case report of a normal child, born after voriconazole treatment of the mother in the second and third trimester (Shoai Tehrani 2013).

Recommendation. If a systemic treatment with an azole derivative becomes absolutely necessary, fluconazole and itraconazole are to be preferred as the better-tested medications. If possible, treatment should start after the first trimester. An inadvertent exposure during pregnancy does not require a risk-based termination or invasive diagnostic, but a detailed ultrasound examination should be carried out (Chapter 1.15).

Azole antifungals for topical use

A multitude of poorly resorbed topical azole derivatives are available for the treatment of superficial fungal infections. The drugs of this group that had been introduced first, namely *clotrimazole* and *miconazole*, are most thoroughly investigated for use in pregnancy. Regarding clotrimazole, there are extensive studies about the treatment of vaginal yeast infections that do not indicate an embryotoxic potential (e.g. Czeizel 1999b, King 1998). Also, there is no suggestion that there is an increase in miscarriages. Czeizel (2004a) noted a decrease in prematurity when vaginosis was treated locally with clotrimazole. Experiences with several thousand pregnant women are available for miconazole (e.g. Czeizel 2004b, McNellis 1977). A suggestion by the Hungarian Malformation Registry about a link between vaginal therapy with miconazole plus metronidazole during the second and third gestational month, and an increase in syndactyly and hexadactyly, has not been substantiated by other studies (Kazy 2005a).

An Israeli report describes two cases of severe skeletonal anomalies after the use of *bifonazole* that are reminiscent of anomalies seen after systemic use of fluconazole. In the first case, bifonazole was taken orally from week 6 to 16, in the second case 500 mg/d vaginally throughout pregnancy and clearly at a higher dose than recommended (Linder 2010). At dose levels which are reached with nomally recommended topical application no teratogenic risks have been noted, yet systematic studies are lacking.

For *ketoconazole* see above (azole antifungals for systemic use).

Clearly less experience has been collected about the local applications of *butoconazole*, *croconazole*, *econazole*, *fenticonazole*, *isoconazole*, *omoconazole*, *oxiconazole*, *sertaconazole*, *sulconazole*, *terconazole*, and *tioconazole*. Teratogenic effects have not been observed (King 1998). This was confirmed for vaginal econazole treatment in a study of 68 pregnant patients (Czeizel 2003a).

Recommendation. Clotrimazole and miconazole belong to the local antifungal medications of choice in pregnancy. The other azole derivates are antimycotic drugs of second choice.

2.6.18 Amphotericin B

Amphotericin B is a broad-spectrum antifungal agent of the polyene group. It binds to ergosterol at the cell membrane of fungi and disturbs cell wall permeability. It can be used intravenously, orally, and locally. With oral application, it is poorly resorbed and thus has only a local effect in the intestinal tract. Conventional amphotericin B given parenterally has a number of side effects, primarily nephrotoxicity. Newer lipid formulations of amphotericin B such as liposomal amphotericin B are characterized by a markedly better tolerance and less nephrotoxicity.

Amphotericin passes the placenta. Relevant plasma concentrations could be measured in a newborn, although the mother had taken her last dose four months prior (Dean 1994). This could be due to placental accumulation or delayed elimination by the fetal kidneys.

Several case reports do not indicate an increased risk of malformations with amphotericin B (e.g. Costa 2009, Ely 1998, King 1998). More than 10 pregnancy courses with liposomal amphotericin B also argue against an embryo- or fetotoxic risk (e.g. Mueller 2006, Pagliano 2005, Pipitone 2005). These experiences are insufficient for a differentiated risk assessment.

As resorption is minimal with oral or local use, a risk appears unlikely.

Recommendation. Amphotericin B should only be used parenterally in cases of serious disseminated fungal infections. The liposomal formulation may be preferred. If treatment took place in the first trimester, a detailed ultrasound examination should be offered to ascertain the normal development of the fetus. Oral and local use of amphotericin B is acceptable in pregnancy.

2.6.19 Echinocandins

Echinocandins are a new antifungal medication group. These parenteral synthetic lipopeptides inhibit the synthesis of 1,3-β-D-glucan, a key ingredient of the fungal cell wall. *Anidulafungin*, *caspofungin*, and *micafungin* are currently approved.

In animal experiments echinocandins cross the placenta. There have been no reports of their use in pregnancy. Yalaz (2006) described the successful postnatal application of caspofungin in a dystrophic premature newborn of the twenth-seventh gestational week.

Recommendation. As there is insufficient data regarding the use of echinocandins in pregnancy, they should only be used where no alternatives are available and the mycosis is life-threatening. If treatment took place in the first trimester, a detailed ultrasound examination should be offered to ascertain the normal development of the fetus.

2.6.20 Flucytosine

Flucytosine is effective against *Cryptococcus neoformans* and many Candida species. It inhibits the DNA synthesis. Within the mycotic cell flucytosine is partially converted into the cytostatic 5-fluorouracil. To a smaller degree this reaction has to be expected in humans as well. Due to a high incidence of resistance, flucytosine should only be administered in combination with another antifungal drug such as amphotericin B.

In animal experiment, fluycytosine has a teratogenic effect at doses below those used in humans. As yet, no malformations have been reported in humans; however, there is, as yet, no published experience with the use of flucytosine in the first trimester. Case reports about application in the second and third trimester for dangerous disseminated cryptococcosis have not shown evidence of fetal damage (e.g. Ely 1998).

Recommendation. Flucytosine should only be used for life-threatening disseminated fungal infections during pregnancy. As it is not indicated as a monotherapy, it needs to be assessed critically if its use as a second mycotic drug is really necessary. If treatment took place in the first trimester, a detailed ultrasound examination should be offered to ascertain the normal development of the fetus.

2.6.21 Griseofulvin

Griseofulvin is an organically derived antifungal agent that is used orally for several weeks against fungal infections of the skin, hair and nails. As it is deposited within the keratin, it is especially suited for the management of fungal infections of nail mykoses.

In animal experiments griseofulvin is teratogenic and, at high doses, cancerogenic. It crosses the placenta at term (Rubin 1965). One publication, based on birth defects data, reported two pairs of conjoined twins after the use of griseofulvin in early pregnancy (Rosa 1987). This observation could not be confirmed in other publications (Knudsen 1987, Metneki 1987). A population based case-control study with some 31 exposed pregnant women did not demonstrate an increased risk of malformations (Czeizel 2004c). These experiences are insufficient for a differentiated risk assessment.

Recommendation. As griseofulvin is not used to treat life-threatening fungal infections, its application in pregnancy should be avoided. If treatment took place in the first trimester, a detailed ultrasound examination should be offered to ascertain the normal development of the fetus.

2.6.22 Terbinafine

Terbinafine is used for both oral and topical treatment of fungal infections of the nails and other dermatophytoses. A prospective study reported on 54 pregnant women exposed to terbinafine which showed no evidence of a teratogenic potential (Sarkar 2003). Of these women 24 were exposed during the first trimester and 26 had an oral exposure. These data are insufficient for a differentiated risk analysis. When used topically, less than 5% is resorbed making a risk unlikely.

Recommendation. Terbinafine should be avoided during pregnancy as safety data are lacking and fungal nail infections do not require urgent treatment. If treatment took place in the first trimester, a detailed ultrasound examination should be offered to ascertain the normal development of the fetus. A topical application is likely to be harmless.

2.6.23 Topical antifungal agents

Regarding the topical use of azole derivatives such as *clotrimazole* and *miconazole*, see Section 2.6.17; for amphotericin B, Section 2.6.18; and for terbinafine, Section 2.6.22.

Nystatin is an antifungal drug from the polyene group. Like the closely related amphotericin B it binds with ergosterol of the mycotic cell wall and interferes with its function. Nystatin is an effective local antifungal drug for candidiasis of the skin or mucosa. When taken orally, it is poorly resorbed and only works locally in the intestinal tract. The indication for intestinal cleansing needs to be critically assessed in immunocompromized patients.

Nystatin is used frequently, and there is no evidence of embryo- or fetotoxic effects (e.g. King 1998). A population-based case control study did not show an increased risk of malformation after first trimester exposure. When treatment was performed in the second and third trimester, slightly more cases of hypospadia were noted (Czeizel 2003b). However, a low resorption rate, methodological weaknesses of the study, and the low number of only 106 pregnant women place the result in question.

A retrospective study of the Hungarian malformation register, with 160 exposed subjects, did not reveal signs of an increased risk of malformation when *natamycin* was applied vaginally (Czeizel 2003c). Based on the same register, a case-control study discussed a possible association between cardiovascular malformations and maternal use of *tolnaftate* in pregnancy (Czeizel 2004d). This observation was based on 26 exposed cases, of which four cases had varying types of cardiac defects (OR 3.1, 95%; CI 1.0–9.7). These data are insufficient for a differentiated risk analysis.

Amorolfine, *butenafine*, *ciclopirox*, *haloprogin*, *naftifin*, and *tolciclate* are insufficiently investigated with regard to prenatal human toxicity. As yet, there is no substantial indication for an increased risk of malformations after local use.

Recommendation. Nystatin, like clotrimazole and miconazole is an antifungal drug of choice during pregnancy. Where possible, these drugs should be preferred. External treatment with amorolfine, butenafine, ciclopirox, haloprogin, natamycin, naftifin, tolciclate, and tolnaftate should be avoided during pregnancy.

2.6.24 Anthelmintics

More than 2 billion people are infected with helminths worldwide. Soil-transmitted helminths have been recognized as an important public health problem in many developing countries. Severe hookworm and other helminth infections during pregnancy may cause anemia, reduced birth weight and increased perinatal mortality. A routine application of anthelmintics during the second and third trimester for women in areas endemic for hookworm infection has been suggested, with the argument that this may improve maternal anemia, birth weight, and neonatal mortility (e.g. WHO 2013c, Christian 2004). However, a randomized placebo-controlled study showed no advantage for newborns whose pregnant mothers had received albendazole or praziquantel (Webb 2011). Recently, it has been discussed if routine anthelmintic treatment during pregnancy might lead to an increased risk for allergies in infancy (Mpairwe 2011).

▶ Benzimidazole anthelmintics

The benzimidazole derivatives *albendazole*, *flubendazole*, *mebendazole*, *thiabendazole*, and *triclabendazole* inhibit the uptake of glucose and thereby kill the parasites. In animal experiments benzimidazole derivative with anthelmintic activity showed teratogenic effects.

Albendazole and *mebendazole* are poorly resorbed from the gastrointestinal tract, except when there is an inflammation. However, enteral absorption may be increased due to high-fat diet. Mebendazole is a highly effective and well tolerated anthelmintic drug used against nematodes (such as pinworms, roundworms, whipworms, and hookworms). There have been reports describing children with various malformations after *in utero* exposure to mebendazole, but a distinct pattern of malformations could not be discerned (review by Schardein 2000). An increased risk of congenital malformations was not observed in a study of over 400 pregnant women exposed to mebendazole in the first trimester (de Silva 1999). This was confirmed in a controlled prospective study covering 192 first trimester exposed pregnant women (Diav-Citrin 2003). Another study with 48 first trimester exposures also found no increased risk for malformations or miscarriages (McElhatton 2007). Although numbers are too small for any definite conclusion, mebendazole does not appear to represent a major teratogenic risk. Significantly more experience has been collected with exposure during the second and third trimester showing no evidence of a fetal risk (e.g. Gyorkos 2006).

Albendazole is a newer, highly effective broad-spectrum anthelmintic which combined with operative interventions has become the treatment of choice for alveolar and cystic echinococcosis. Limited experience in the first trimester has not shown evidence of a major risk (Gyapong 2003, Cowden 2000). There are several thousand pregnancies with the use of albendazole in the second or third trimester without any obvious adverse reactions reported (e.g. Webb 2011, Ndyomugyenyi 2008).

Two abstracts from Korea which reported the outcome of 16 pregnant women after the first trimester exposure to *flubendazole* showed no evidence of a teratogenic potential (Choi 2008, 2005). However, the data is insufficient for a differentiated risk assessment.

There are no reports of *thiabendazole* and *triclabendazole* use during human pregnancies.

Recommendation. Mebendazole may be used during pregnancy to treat relevant worm diseases. Albendazole may be used in cases of echinococcosis. The other benzimidazole anthelmintics should only be used with a compelling indication, and when more established anthelmintics are ineffective. After first trimester exposure a detailed ultrasound examination should be offered to ascertain the normal development of the fetus.

Ivermectin

Ivermectin is a broad-spectrum anthelmintic agent which is mainly used in humans in the treatment of onchocerciasis (river blindness), lymphatic filiriasis and strongyloidiasis. It is also effective against other worm infections and some epidermal parasitic skin diseases, such as scabies. Ivermectin is well resorbed after oral administration. Animal experiments do not suggest a teratogenic potential, although at maternally toxic exposures malformations were noted in rodents. A number of case reports describing accidental treatments during the first trimester have not shown malformations in the children (Gyapong 2003, Chippaux 1993, Pacque 1990). However, data are insufficient for a differentiated risk assessment. A study encompassing more than 100 women who took ivermectin during the second trimester found no significant anomalies in the newborns (Ndyomugyenyi 2008).

Recommendation. With a compelling indication ivermectin may be used in pregnancy. After first trimester exposure a detailed ultrasound examination should be offered to ascertain the normal development of the fetus.

Niclosamide

Niclosamide is an anthelmintic that is effective against tapeworms (cestodes). It affects the energy metabolism of the parasites and is practically not resorbed by the intestinal tract. This agent had been used extensively in the past and is not suspected to cause malformations, but has not been systematically studied in humans.

Recommendation. Niclosamide may be given during pregnancy to treat relevant tapeworm infections. Application in the first trimester needs to be critically assessed as tapeworm infections are generally not a great hazard to the mother or unborn child. After first trimester exposure, a detailed ultrasound examination should be offered to ascertain the normal development of the fetus.

Praziquantel

Praziquantel is a highly effective broad-spectrum anthelmintic agent against many trematodes and cestodes. It is mainly used for the treatment of schistosomiasis (bilharziosis). No teratogenicity has been reported in animal studies. Over the last decades millions of pregnant women have been inadvertently treated with praziquatel during routine anthelmintic programs without an obvious adverse reactions reported. A few publications

also found no evidence of a teratogenic potential after mothers had been treated in the first trimester (Adam 2004a, Paparone 1996). In a study from Uganda encompassing more than 1,000 pregnant women, treatment with praziquantel in the second and third trimester was not associated with an increase in adverse outcomes (Ndibazza 2010). The WHO (2002) recommends the use of praziquantel for schistosomiasis during pregnancy.

Recommendation. Praziquantel should be reserved for specific severe indications like schistosomiasis. Usually for other indications better-established anthelmintics are available. After first trimester exposure a detailed ultrasound examination should be offered to ascertain the normal development of the fetus.

▶ Pyrantel

Pyrantel is a broad-spectrum anthelmintic that acts by inhibition of cholinesterase, causing spastic paralysis and subsequent death of the parasite. No teratogenicity has been reported in animal studies. Pyrantel is poorly absorbed from the gastrointestinal tract. Published experience on its use during pregnancy is not sufficient to determine risk.

Recommendation. Pyrantel should be avoided in pregnancy because better tested alternatives are available for all indications. After first trimester exposure a detailed ultrasound examination should be offered to ascertain the normal development of the fetus.

▶ Pyrvinium

Pyrvinium is effective against pinworms (enterobius). After oral administration it is hardly absorbed. Therefore, it is unlikely to reach the fetus in relevant amounts. There are no reports of embryo- or fetotoxic effects. However, there has been no published experience with the use of pyrvinium during pregnancy. A Danish cohort study based on prescription registers identified 1606 women redeeming a prescription for pyrvinium (449 during first trimester). The pregnancy outcome was not considered in this article (Torp-Pedersen 2012).

Recommendation. Pyrvinium may be used during pregnancy.

▶ Other anthelmintics

Diethylcarbamazine is used for the treatment of filiriasis and onchocercosis. No teratogenicity was reported in animal studies. No publications regarding its use during human pregnancies have been located.

Levamisole is used as anthelmintic and as an immunomodulator. A retrospective study with data from the Hungarian Malformation Registry based on 14 subjects (four first trimester exposures), shows no evidence of an increased risk of malformations after use of levamisole (Kazy 2004).

Oxamniquine is used for the treatment of schistosomiasis. No experiences have been reported about its use during pregnancy.

Recommendation. Diethylcarbamazine, levamizole and oxamniquine should be avoided during pregnancy as better tested alternatives are available for most indications. After first trimester exposure a detailed ultrasound examination should be offered to ascertain the normal development of the fetus.

2.6.25 Herpes medications

Herpes medication for systemic use

A number of closely related nucleoside analogs are used against viruses of the herpes group. They are effective by blocking the viral DNA polymerase. The affinity of the nucleoside analogs are much lower to human than to viral DNA polymerase.

The standard agent of this group is *acyclovir* which is used against the varicella-zoster virus (VZV) and herpes simplex virus (HSV) type 1 and 2. The manufacturer's case collection contains over 1,000 women treated systemically with acyclovir during pregnancy, 756 of them during the first trimester; with no evidence of embryo- or fetotoxic risk (Stone 2004). A study of a Danish Registry with 1,561 women with prescriptions in the first trimester, showed no increased risk after acyclovir (Pasternak 2010). Although these studies had some methodological weaknesses, the experiences argue against the risk of acyclovir in pregnancy.

Valacyclovir, the prodrug of acyclovir, is converted quickly and completely to acyclovir in the body. Orally it is distinctly better resorbed than acyclovir of which only about 20% is resorbed. The manufacturer did not find an increased risk of malformation in 56 women who had received valacyclovir during pregnancy, 14 of these during the first trimester (Glaxo Wellcome 1997). Also, the above cited study of the Danish Registry did not show evidence of embryo- or fetotoxic risk in 299 pregnancies, in which the mother filled a prescription for valacyclovir during the first trimester (Pasternak 2010).

Ganciclovir and its prodrug *valganciclovir* are effective in cytomegalus virus infections (CMV). In animal experiment, teratogenic effects were only seen with plasma levels that were twice as high as those recommended in human therapy. There are a few case reports describing normal pregnancy outcome after the first trimester treatment during early pregnancy (Pescovitz 1999). Puliyanda (2005) describes a successful oral treatment with ganciclovir for an intrauterine CMV infection after the 22nd week. These experiences are insufficient to evaluate the safety of ganciclovir in pregnancy.

Famciclovir is quickly converted after enteral resorption into the virostatic *penciclovir*. Neou (2004) reported a newborn whose mother took 250 mg famciclovir daily in her fifth week. The boy who succumbed to a severe neonatal infection had a hypoplastic thymus, a mild stenosis of the pulmonary valve, an ostium secundum defect, and an enlarged liver with stenotic extrahepatic biliary ducts. A retrospective study of data from the Danish Birth Registry contained 26 women who took oral famciclovir during the first trimester, and showed no increase in the malformation rate (Pasternak 2010).

There is insufficient data about the use in pregnancy for *brivudine*, *cidofovir*, *foscarnet*, and *fomivirsen*. In animal experiments, small doses of foscarnet sodium trigger skeletal anomalies in rats and rabbits.

No experience is reported for the combination therapy of *dimepranol* and *inosine* that is used to stimulate the immune system against viruses of the herpes group.

Recommendation. If an antiviral therapy is indicated for a severe maternal disease, or to protect the fetus from an intrauterine infection, acyclovir or valacyclovir should be used as the best evaluated medication whenever possible. The other antiviral agents are only indicated in infections where they have a therapeutic advantage over acyclovir. After the application of one of the less well examined drugs during first trimester, a detailed ultrasound examination should be offered to ascertain the normal development of the fetus.

Herpes medication for local use

Acyclovir, *foscarnet*, *ganciclovir*, *idoxuridine*, *penciclovir*, *trifluridine*, and *tromantadine* are locally applied in HSV infections. None of these agents has been suspected to give rise to teratogenic effects.

Acyclovir may be used in pregnancy systemically and is harmless in local application. In the above cited Danish Registry study 2,850 women had used acyclovir and 118 women penciclovir locally during the first trimester, and no increased malformation risk was noted (Pasternak 2010). The other agents lack studies about local application.

Docosanol is a newly approved agent for topical application in herpetic cold sores. The mechanism of action is unknown. There has been no experience about its use in pregnancy; however, a risk is unlikely with its minimal resoption.

The local application of *zinc sulfate* and of patches containing hydrocolloid particles is harmless in pregnancy.

Recommendation. Where indicated, local remedies for herpes may be used during pregnancy. Drying agents and patches for herpes are harmless. Where possible, acyclovir should be preferred as the best evaluated antiviral drug.

2.6.26 Antiviral drugs for hepatitis

Antiviral drugs for hepatitis B

Nucleoside/nucleotide analogs and α-interferon (Chapter 2.12) are used for the management of chronic hepatitis B. A general therapeutic recommendation cannot be made for pregnancy as data are inadequate. Experience so far did not reveal serious signs of teratogenic or fetotoxic damage in humans. If there is a very active Hepatitis B or cirrhosis, antiviral treatment might be considered. Passive–active immunoprophylaxis of infants have reduced mother-to-child-transmissions. However, in high viremic mothers immunoprophylaxis might fail. No consensus has been reached if pregnant women who are HBsAg positive, and highly viremic should be treated in the third trimester to prevent a perinatal transmission to the infant (e.g. Pan 2012).

For lamivudine and tenofovir see Section 2.6.30.

Adefovir dipivoxil, the prodrug of adefovir, is an orally-administered nucleotide analog. No teratogenicity has been reported in animal studies. The Antiretroviral Pregnancy Registry (2013) received reports of 48 births after a maternal adefovir dipivoxil regimen in the first trimester. No birth defects were observed in the infants.

Entecavir has shown teratogenic effects in animal studies where, in high doses, more vertebral and tail malformations occurred. Of 55

infants whose mothers were exposed to entecavir during first trimester, two babies were born with birth defects (no details available) (Antiretroviral Pregnancy Registry 2013). One case report describes a healthy baby born after entecavir exposure for 32 days in the second trimester (Kakogawa 2011).

Telbivudine raised no suspicions for teratogenicity in animal experiments. Among 86 pregnancies of women who received *telbivudine* before or in early pregnancy the abortion rate was 7.9%. Fifty mothers delivered 52 infants. One pregnancy was terminated because of cleft lip and palate and one infant showed right ear accessories, no other birth defects were reported (Liu 2013). In the Antiretroviral Pregnancy Registry (2013) no birth defects were observed in 10 infants after first trimester exposure to telbivudine.

In a prospective study, 136 infants were born after maternal treatment with telbivudine in late pregnancy to prevent perinatal transmission. Exposure took place from the twentieth to thirty-second gestational week until at least 1 month after delivery. There were no significant differences in infant outcomes compared to a control group. No serious adverse events were noted in the infants (Han 2011). There is an ongoing discussion as to whether telbivudine should be given to women with a high virus load during late pregnancy to prevent intrauterine transmission (review by Deng 2012).

▶ Ribavirin

The nucleoside analog *ribavirin* inhibits both DNA- and RNA-viruses, displaying a relatively broad antiviral spectrum experimentally. Among other applications, it is used to treat respiratory syncytial virus (RSV) infections in infants, and, combined with *α-interferon* (Chapter 2.12), against hepatitis C.

Ribavirin has teratogenic and mutagenic effects in animal experiments. Nine women who were treated during the second half of pregnancy for severe measles delivered healthy infants (Atmar 1992). A woman treated for SARS (severe acute respiratory syndrome) in the first trimester with ribavirin by injection for 3 days gave birth to a normal child (Rezvani 2006). In its Pregnancy Registry, the manufacturer noted eight women with ribavirin exposure in the first trimester, and 77 women with exposure within 6 months of the last menstrual period (Roberts 2010). The authors found no evidence of a teratogenic risk for humans.

In summary, current data is insufficient for a risk assessment for ribavirin. An embryo- or fetotoxic risk is not apparent with the available case reports.

Paternal exposure

The level of ribavirin is twice as high in seminal fluid as in sperm. There has been no increased risk of malformations after paternal ribavirin treatment and interferon in 20 pregnancies reported as case reports (review by Hofer 2010), and 110 pregnancies of the Ribavirin Pregnancy Registry (Roberts 2010). These numbers are inadequate to assess a possible risk after paternal exposure.

▶ Other antiviral drugs for hepatitis C

The protease inhibitors *boceprevir*, *simeprevir* and *telaprevir* have been approved for the treatment of chronic hepatitis C. There are no

experiences with their use in pregnancy. The same applies to *sofosbuvir* – a recently approved polymerase inhibitor for the treatment of chronic hepatitis C.

Recommendation. Ribavirin and the other antiviral agents discussed here should only be used during pregnancy when compellingly indicated. Treatment during the first trimester is not a justification for a risk-based termination of pregnancy (Chapter 1.15). In such a situation a detailed ultrasound examination should be offered to ascertain normal fetal development.

2.6.27 Antiviral drugs for influenza

Amantadine

Amantadine enhances dopamine activity at the receptor and thus is also used as an antiparkinson drug. As an antiviral medication, it inhibits the membrane protein hampering the ability of the virus to enter the cell nucleus. Because of rapid resistance and frequent neurologic side effects, it is not recommended any more as an antiviral agent. For amantadin in Parkinson disease, see Chapter 2.11.

Neuraminidase inhibitors

The neuraminidase inhibitors *oseltamivir*, *peramivir* and *zanamivir* are used to treat patients whose influenza requires therapy.

Oseltamivir has not shown teratogenic effects in animal studies. A prospective investigation at two Japanese centers did not see an increase in malformations where 90 women had been treated in the first trimester (review by Tanaka 2009). Another study involving 137 exposed offspring, 18 of them in the first trimester, also did not find a higher risk (Greer 2010). The manufacturer, too, noticed no increased risk in 115 women who had used oseltamivir during pregnancy, 44 of these during the first 3 months (Donner 2010). One study with 81 pregnant women exposed to oseltamivir, 24 in the first trimester, found an increased risk of late transient hypoglycaemia compared to an unexposed control group. No other increased risks of adverse birth outcomes among the infants have been observed. One child had a ventricular septal defect. This was the only major malformation after exposure in the first trimester (Svensson 2011). Another publication included 619 pregnant women exposed to oseltamivir, 159 of them in first trimester. The overall rate of major malformation after first trimester exposure was 1.3% (Saito 2013). In a French publication, a total of 337 mothers received at least one prescription of oseltamivir during pregnancy. One congenital heart defect was observed among 49 infants who were exposed during first trimester. No significant association between adverse fetal outcomes and exposure to oseltamivir during pregnancy could be found (Beau 2014). Dunstan (2014) could also find no signs of embryo- or fetotoxic effects in 27 exposed pregnant women. No birth defects were observed in eight first trimester exposures. A population-based retrospective cohort study analyzed data from 1,237 women who received oseltamivir during pregnancy. Compared to a control group, there were no associations between maternal use of oseltamivir with preterm birth and low Apgar score. Women who

took oseltamivir during pregnancy were less likely to have a small for gestational age infant. However, birth defects and time of exposure were not mentioned (Xie 2013).

Two studies looked into the pharmacokinetics of oseltamivir and its active metabolite oseltamivir carboxylate during gestation. Greer (2011) compared the pharmacokinetics of 10 pregnant women in each group during the last trimester and found no significant differences. Beigi (2011) examined the pharmacokinetcs in 16 pregnant women (average gestational age 24.6 weeks) in comparison to 23 nonpregnant women, and found the pregnant group to have lower oseltamivir carboxylate level. However, it remains unclear if the dose needs to be adjusted during pregnancy.

Zanamivir is applied by inhalation and very little is resorbed. No teratogenicity was found in animal experiments. A case series study from Japan reported 50 infants born after intrauterine zanamivir exposure, 15 of them were exposed in the first trimester. No malformations have been observed (Saito 2013). A prospective surveillance study did not provide a case that use of zanamivir in pregnancy is associated with an increased risk of adverse pregnancy outcomes among 180 women exposed to zanamivir during pregnancy. No major malformations were reported in 37 zanamivir first trimester exposures (Dunstan 2014). Experience and the presence of low systemic concentrations, make it unlikely that there is an increased embryo- or fetotoxic risk.

Experience during pregnancy with *peramivir* is insufficient for a risk assessment.

Recommendation. If indicated, neuraminidase inhibitors oseltamivir and tanamivir may be used in pregnancy. Peramivir should be avoided. Amantadine is no longer recommended for the treatment of influenza. When used during the first trimester, a detailed ultrasound examination should be offered to ascertain normal fetal development.

2.6.28 Antiretroviral agents

The aim of *antiretroviral therapy* (ART) during pregnancy is the prevention of a vertical transmission of the *human immunodeficiency virus* (HIV) from mother to child, and also the optimal management of the HIV-infected mother, whereby unwanted side effects are to be kept at a minimum for her and the child. ART in pregnancy has become an integral part in the prophylaxis of HIV transmission after data revealed the protective effect of perinatal prophylaxis, with the nucleoside analog reverse transcriptase inhibitor (NRTI) *zidovudine* that could prevent a possible vertical transmission during the last trimester and labor (Connor 1994). National and international guidelines recommend a standard therapy for both nonpregnant and pregnant HIV-infected women take a combination of at least three antiretroviral medications (EACS 2013, OARAC 2012, WHO 2010c). This *highly active antiretroviral therapy* (HAART) typically consists of two NRTIs and either a protease inhibitor (PI), or a non-nucleoside analog reverse transcriptase inhibitor (NNRTI). The intention is that the suppression of the plasma HIV load (HIV-RNA) should be as close to <50 copies/mL at least by the end of the pregnancy. When an effective HAART is applied during pregnancy and lactation, the HIV rate of transmission can be decreased from its former levels of

20–30% to <1% (Townsend 2008, Warszawski 2008). The decision of what regimen to use is already complicated in nonpregnant patients, but more so in pregnancy. How to balance individual needs and risks should be considered, especially in view of the timing of the start of treatment, a possible interruption of therapy during the first trimester in women already under treatment, and the selection of appropriate antiretroviral medications.

The risks from intrauterine exposure to combinations of antiretroviral agents are difficult to assess, as data are limited concerning the pharmakinetics and the developmental toxicity for most of the drugs. There is no data about the long-term toxicity of the exposure to intrauterine retroviral substances. Information about the safety of retroviral drugs in pregnancy are limited to experiments in animals, single case reports, a few clinical studies, and analyses of registries such as the Antiretroviral Pregnancy Registry (2013) in the USA that contains most of the information about the safety of antiviral substances in pregnancy.

2.6.29 Overview of the antiretroviral medications

Five groups of antiviral substances are distinguished:

1. Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs): *abacavir*, *didanosine*, *emtricitabine*, *lamivudine*, *stavudine*, *tenofovir*, and *zidovudine*.
2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs): *delavirdine*, *efavirenz*, *etravirine*, *nevirapine*, and *rilpivirine*.
3. Protease inhibitors (PIs): *atazanavir*, *darunavir*, *fosamprenavir*, *indinavir*, *lopinavir*, *nelfinavir*, *ritonavir*, *saquinavir*, and *tipranavir*.
4. Entry inhibitors: *enfuvirtide* and *maraviroc*.
5. Integrase inhibitors: *raltegravir*, *dolutegravir* and *elvitegravir*.

Data currently available do not allow for a summarizing differentiated risk analysis for antiretroviral medications in pregnancy. With the exception of efavirenz, there have been no serious signs of teratogenic or fetotoxic damages in humans (e.g. Watts 2011, ECS 2003). Prospectively documented pregnancies do not demonstrate a higher risk of malformations and, like retrospective case reports, fail to reveal any distinct pattern of anomalies. When antiretroviral agents are used in the first trimester, the embryotoxic risk appears to be generally small (Phiri 2014, Floridia 2013, Antiretroviral Pregnancy Registry 2010, Joao 2010). Nevertheless, substances that might be embryotoxic should be eschewed in early pregnancy. Common side effects in children treated *in utero* or after birth with zidovudine or antiretroviral combinations consist of hematologic problems, especially anemias and neutropenias (Dryden-Peterson 2011, Feiterna-Sperling 2007, Le Chenadec 2003). It is being debated if antiretroviral treatment with or without protease inhibitors favors prematurity (Chen 2012, Patel 2010, Kourtis 2007, Cotter 2006, Tuomala 2005). The maternal risks of therapy are discussed with the specific medications.

The medical treatment of HIV infection during pregnancy is a prime example for the need to sometimes utilize insufficiently tested medications – because of the acute danger for mother and child. In individual cases it needs to be critically assessed if an ongoing or maternally indicated treatment is absolutely necessary during the time of embryogenesis, or if it can be temporarily suspended.

Recommendation. Antiretroviral medications may be used in pregnancy. Specific risks for the prophylaxis of transmission and the therapy of maternal HIV infection need to be observed. The choice of medication and the timing of treatment have to be decided on an individual basis. When choosing medications it should be noted that some of the retroviral substances should be avoided during pregnancy, if possible. This concerns efavirenz (teratogenic effects) and the combination stavudine/didanosine (lactic acidosis). For newer medications such as maraviroc, raltegravir and etravirine, few or no data are available concerning their use in pregnancy. Caution is called for when nevirapine is used in women with CD4 cell counts of <250/mm mm^3 (hepatotoxicity). If nevirapine is used during pregnancy, transaminases need to be checked regularly, especially during the first 18 weeks of treatment; also, clinical symptoms are to be watched. The short-term use of nevirapine for transmission prophylaxis does not seem to carry a similar risk.

When exposure occurs during the first trimester, a detailed ultrasound examination should be offered to ascertain the normal development of the fetus. It is recommended that the pregnant patient is cared for in a specialized center. Physicians should report pregnancies involving the use of HIV medications shortly after diagnosis to the Antiviral Pregnancy Registry (www.APRegistry.com).

2.6.30 Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)

Data from clinical studies during pregnancy in women are available for *abacavir*, *didanosine*, *emtricitabine*, *lamivudine*, *stavudine*, *tenofovir*, and *zidovudine*. With the exception of didanosine, the NRTIs showed comparable levels in the maternal serum, and the umbilical cord blood suggested an easy placental passage (Pacifici 2005). Having an affinity to mitochondrial γ-DNA polymerases, NRTIs can induce mitochondrial dysfunction. The greatest risk for mitochondrial toxicity is exhibited *in vitro* for didanosine, stavudine, and zidovudine. The question if a perinatal NRTI exposure could lead to mitochondrial problems in children is currently under discussion; a final consensus has not been reached (Benhammou 2007, Blanche 1999).

Lamivudine and zidovudine are the NRTIs that should be preferred during pregnancy because of extensive experience. Abacavir, emtricitabine and tenofovir are alternative NRTIs which also might be used. Didanosine and stavudine should only be used in special circumstances (OARAC 2012).

Abacavir

Abacavir can lead to skeletal anomalies when given to rats at a high dosage. There is no evidence of teratogenicity in humans. Abacavir readily crosses the placenta (Chappuy 2004). Data from the Antiretroviral Pregnancy Registry (2013) with 27 birth defects in 905 cases, indicate a malformation rate of 3.0% after exposure during the first trimester, similarly as seen in the general population of the USA.

Didanosine

In animal experiments *didanosine* given at high doses did not show teratogenic effects. Didanosine crosses the placenta only in limited

amounts (Wang 1999). The data of the Antiretroviral Pregnancy Registry (2013) show a slightly increased malformation rate after first trimester exposure at 4.8% (20 of 416 births), in comparison to 2.7% in the general US population. However, no distinct pattern of birth defects has been discovered. In a study where 14 HIV infected women were treated at 26–36 weeks with didanosine, neither maternal nor neonatal side effects were noted (Wang 1999). Cases of lethal lactic acidosis have been described in pregnant women treated with a combination of stavudine and didanosine (Mandelbrot 2003, Sarner 2002). Due to the risk of fatal lactic acidosis, combination treatment with didanosine and stavudine should only be used in cases where no alternatives are available (Bristol-Myers Squibb 2001).

Emtricitabine

Emtricitabine has not shown evidence of teratogenicity in animal experiments or in humans. It crosses the placenta readily (Stek 2012, Hirt 2009b). Among cases of first trimester exposures reported to the Antiretroviral Pregnancy Registry (2013), the prevalence of birth defects was 2.4% (34 of 1,400 births), similar to the rate in the general US population.

Lamivudine

Lamivudine, one of the best evaluated NRTIs, is also approved for the treatment of chronic hepatitis B. Levels measured in the umbilical cord blood correspond to those of the mother. Data from the Antiretroviral Pregnancy Registry (2013) indicate an unsuspicious malformation rate of 3.1% (136 of 4,360 births). A larger study to prevent perinatal transmission was conducted in France where 445 pregnant women received zidovudine and lamivudine after gestational week 31, and their newborns were also given the combination for 6 weeks (Mandelbrot 2001). In this study newborns displayed significant side effects that included lethal mitochondriopathies. However, lamivudine and zidovudine are medications that are preferred in pregnancy because of extensive experience.

Stavudine

There is no evidence that *stavudine* leads to teratogenic effects in animal experiments or humans. Stavudine crosses the placenta easily (Chappuy 2004). The malformation rate after exposure in the first trimester is 2.6% (21 of 805 births) according to data from the Antiretroviral Pregnancy Registry (2013), thus similar as in the general US population (2.7%). Good tolerance of a staduvine–lamivudine combination has been described in a small phase I/II study with 14 mother–child pairs (Wade 2004). Cases of lethal lactic acidosis have been described in pregnant women treated with a combination of stavudine and didanosine (Mandelbrot 2003, Sarner 2002). Due to the risk of a fatal lactic acidosis, combination treatment with didanosine and stavudine should only be used in cases where no alternatives are available (Bristol-Myers Squibb 2001).

Tenofovir

In animal experiments, offspring of monkeys that received high doses of *tenofovir* have a decreased fetal growth rate and diminished fetal bone density (Tarantal 2002). During pregnancy tenofovir crosses the placenta easily (Flynn 2011, Hirt 2009a). There is no evidence that tenofovir is teratogenic in humans. According to the data of the Antiretroviral Pregnancy Registry (2013) the malformation rate after exposure during the first trimester is 2.3% (46 of 1,982 births), similar to the 2.7 % rate in the general US population. In clinical studies HIV patients, primarily children, displayed decreased bone density when treated with tenofovir. The clinical significance of these findings is still unclear. One study did not reveal any risk for adverse effects of *in utero* tenofovir exposure in 141 pregnant women (Gibb 2012). However, tenofovir should be used with caution during pregnancy, because of the risk of fetal bone changes and the paucity of other data about its pregnancy-related risks.

Zidovudine

Zidovudine, also known as *azidothymidine* (AZT), is the oldest antiviral drug used for antiretroviral therapy. It readily crosses the placenta. In rats, maternal toxic doses lead to an increased malformation rate during organogenesis, an effect not seen with lower doses. There are no signs of teratogenicity in humans. According to data from the Antiretroviral Pregnancy Registry (2013) the malformation rate of 3.2% (129 of 4,000 births) was not significant higher than that of the general US population. The application of zidovudine has been well studied in pregnancy and is considered to be safe in regard to short-term and medium-term toxicities. A common side effect, when zidovudine is used in the perinatal period, is a transient anemia in newborns (Sperling 1998, Connor 1994). A follow-up study of 234 children who had been exposed to zidovudine *in utero* did not display any physical, immunological, or cognitive anomalies. The median age of children at the time of last follow-up was 4.2 years (range, 3.2–5.6 years) (Culnane 1999). Also, there was no evidence of an increased risk for neoplasia in more than 700 children after pre- and perinatal exposure (Culnane 1999, Hanson 1999). There are no data regarding long-term toxicity, especially for cancerogenicity.

2.6.31 Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Data from clinical studies about the safety in human pregnancy for NNRT is are limited. *Nevirapine* is the agent that should be preferred if a NNRTI is required during pregnancy. *Efavirenz* might be used in special circumstances. For *etravirine* and *rilpivirine* the data are insufficient to recommend use during pregnancy (OARAC 2012). *Delavirdine* is not recommended as part of an initial therapy.

Delavirdine

Delavirdine caused an increased incidence of ventricular septal defects in rats. Experience in humans is limited to 11 births after first

trimester exposure reported to the Antiretroviral Pregnancy Registry (2013). Although no birth defects have been observed, these data allow no differentiated risk analysis. Most guidelines do not recommend delavirdine as a part of antiretroviral regimens for initial treatment of HIV infection because of inferior efficacy.

Efavirenz

In animal experiments *efavirenz* showed evidence of teratogenicity. Three of 20 prenatally exposed cynomolgus monkeys showed malformations when plasma levels were similar to the therapeutic levels in humans. Anencephaly with unilateral anophthalmia was observed in one fetus, microphthalmia in another, and cleft palate in a third. There are case reports in humans about neural tube defects in children whose mothers had received efavirenz during the first trimester (de Santis 2002, Fundaro 2002). According to the data of the Antiretroviral Pregnancy Registry (2013) the malformation rate of 2.3% (18 of 766 births) after first trimester exposure is comparable to the background rate of 2.7% in the general US population. The 18 birth defects included one infant with myelomeningocele. Another child was born with anophthalmia, severe facial cleft and amniotic banding. In total, the Antiretrorviral Pregnancy Register received six retrospective reports of neural tube defects; four of them were exposed to efavirenz.

A meta-analysis, including nine prospective studies together with 1,132 live births, did not detect an increased risk of overall birth defects after exposure to an efavirenz-containing regimen during the first trimester. Including retrospective studies, one neural tube defect was reported in 1,256 live births (Ford 2010). An update of this meta-analysis which included 181 additional subjects had similar results (Ford 2011).

In contrast to these reassuring findings, another study analyzes data of 1,112 infants born between 2002 and 2007. A significantly increased risk of congenital anomalies after exposure to efavirenz during first trimester was observed. Six of 47 infants with first trimester exposure to efavirenz had congenital anomalies (adj.OR 2.84, 95%; CI: 1.13–7.16) (Knapp 2012). However, the six observed major and minor defects (patent foramen ovale, gastroschisis, postaxial polydactyly, Arnold-Chiari malformation, talipes equinovarus, plagiocephaly), do not present a distinct pattern.

With the available published experience, the British HIV Association guidelines panels concluded that there are insufficient data to support the former position and furthermore recommend that efavirenz can be both continued and commenced in pregnancy (Taylor 2012). However, the United State guidelines are more restrictive. They recommend that an efavirenz-based regimen may be continued in women who present for antenatal care in the first trimester, provided the regimen produces virologic suppression (OARAC 2012).

Etravirine

Animal experiments have not shown that *etravirine* is teratogenic. Experience in pregnancy is limited to case reports (Jaworsky 2010, Furco 2009). According to the data of the Antiretroviral Pregnancy Registry (2013) no birth defects were reported in 39 infants born after first trimester

exposure to etravirine. Experiences are insufficient to analyze a possible risk in pregnancy.

Nevirapine

There is no evidence in animal experiments or human experience that *nevirapine* is teratogenic. Nevirapine crosses the placenta easily and attains levels in the neonate that correspond to those of the mother (Benaboud 2011, Mirochnick 1998). According to the data of the Antiretroviral Pregnancy Registry (2013) the malformation rate after first trimester exposure is 2.9% (31 of 1,061 births), which is no higher than that of the general US population.

Studies indicate that viral transmission is blocked when 200 mg p.o. nevirapine is given to the mother at the beginning of labor, and the newborn receives a single dose of 2 mg/kg 48 to 72 hours after delivery (Guay 1999). There is a high risk of developing viral resistance even after a single dose (low resistance barrier and long half-life of nevirapine), thus nevirapine should only be administered in a combination regimen.

Reports have been published describing single cases of liver toxicity in pregnant women who took nevirapine (e.g. Knudtson 2003). This event is often rash-associated and potentially fatal. Liver toxicity is primarily observed in patients with higher CD4 cell counts (>250/mm³); in these patients the risk of symptomatic hepatic events is twelve times greater than in women with lower CD4 cell counts (<250/mm³). Studies indicate that pregnancy *per se* is a risk factor for liver toxicity. Pregnant patients using HAART that includes nevirapin have no higher risk of hepatotoxicity than those who use HAART without nevirapine (Ouyang 2010, Ouyang 2009). These data suggest that the risk of liver toxicity of nevirapine is similar in pregnant and nonpregnant patients. However, if nevirapine is used in pregnancy, physicians should be aware of hepatotoxicity.

Rilpivirine

Animal experiments failed to show that *rilpivirine* is teratogenic. In the Antiretroviral Pregnancy Registry (2013) no birth defects were reported in 31 infants born after first trimester exposure to rilpivirine. One publication describes two healthy infants after rilpivirine exposure during pregnancy (Colbers 2014). Experiences are insufficient to analyze a possible risk in pregnancy.

2.6.32 Protease inhibitors (PIs)

PIs are being used increasingly in pregnancy. They are recommended in regimens combined with two NRTI drugs. PI therapy can lead to the disturbance of glucose tolerance and even to the manifestation or exacerbation of diabetes mellitus. It remains unclear if pregnancy itself increases the risk even further. Generally, PIs pass the placenta poorly (Gingelmaier 2006, Marzolini 2002, Mirochnick 2002). Therefore, fetal toxicity would seem to be unlikely.

Lopinavir/ritonavir and *atazanavir* with low-dose ritonavir boosting are the preferred PIs during pregnancy. Alternative PIs include ritonavir-boosted *saquinavir* and *darunavir*. *Indinavir* and *nelfinavir* should

only be used in special circumstances. Data is too limited to recommend the routine use of *fosamprenavir* and *tipranavir* in pregnant women (OARAC 2012).

Atazanavir

Atazanavir has not shown evidence of teratogenicity in animal experiments or human experience. According to the data of the Antiretroviral Pregnancy Registry (2013), the malformation rate of 2.2% (19 of 878 births) after first trimester exposure is comparable to the rate of 2.7% in the general US population. A number of studies are available, including pharmacokinetic evaluations in pregnant women using HAART with atazanavir (Mirochnick 2011, Ripamonti 2007). Some experts recommend an increased dose in late pregnancy. The umbilical cord blood of neonates shows atazanavir levels of 13–16% of those seen in the maternal serum. Atazanavir inhibits the uridin glucuronosyl transferase that metabolizes indirect bilirubin. Thus, as a common side effect, atazanavir treatment may lead to higher indirect bilirubin levels. While case numbers are relatively small, investigations showed that neonates of atazanavir-treated mothers did not show pathological elevations of indirect bilirubin. (Mirochnick 2011, Ripamonti 2007).

Darunavir

Darunavir did not demonstrate evidence of teratogenicity in animal experiments. Some case reports demonstrated a limited placental transfer. Like with other PIs a reduction in plasma levels has been observed in late pregnancy (Pinnetti 2010). In the Antiretroviral Pregnancy Registry (2013) five birth defects were reported in 212 infants born after first trimester exposure to rilpivirine (prevalence 2.4%). Few experiences about its use in pregnancy are available (e.g. Jaworsky 2010, Ivanovic 2010). These data are insufficient for a differentiated risk assessment.

Fosamprenavir

In animal experiments no evidence was found that *fosamprenavir* leads to teratogenicity. Human data about its use in pregnancy are very limited. Transplacental passage analyzed in seven cases was relatively high compared to other PIs. The authors detected a median ratio of 0.27 of cord blood to maternal amprenavir level (the active metabolite of fosamprenavir) (Cespedes 2013). One publication did not report adverse effects in nine infants after intrauterine exposure to fosamprenavir (Martorell 2010). Two birth defects among 102 births were reported to the Antiretroviral Pregnancy Registry (2013) after first trimester exposure to fosamprenavir. These data are insufficient for a differentiated risk assessment.

Indinavir

Evidence for teratogenicity is not evident for *indinavir* in animal experiments or human reports. Little of indinavir crosses the placenta (Mirochnick 2002). According to the data of the Antiretroviral Pregnancy

Registry (2013) the malformation rate of 2.4% (7 of 289 births) after first trimester exposure is comparable to that in the general US population. These data are insufficient for a differentiated risk assessment. There is a theoretical concern that physiologic hyperbilirubinemia might be exacerbated due to indinavir.

Lopinavir/ritonavir

Lopinavir is used in conjunction with its pharmacological booster ritonavir. In animal experiments with high doses of lopinavir, rats displayed evidence of embryotoxicity with an increased rate of miscarriages, less fetal viability, lower fetal weight, and skeletal changes. These problems were not apparent in rabbits. There is no evidence of teratogenicity in humans. Like most PIs, lopinavir/ritonavir crosses the placenta poorly (Gingelmaier 2006). According to the data of the Antiretroviral Pregnancy Registry (2013) the malformation rate is 2.3% (26 of 1,125 births) after first trimester exposure, and thus not increased in comparison to the general US population. Studies with HIV-infected pregnant women indicate that the treatment with lopinavir/ritonavir is well tolerated. Pharmacokinetic investigations show lower plasma levels, primarilty in the last trimester (Best 2010). It is unclear if pregnant women require a higher dose or just a continuation of the PI standard therapy. A report of 50 infants who received lopinavir/ritonavir after birth observed an association with transient adrenal dysfunction in the infants (Simon 2011). A systematic review about the safety and efficacy of lopinavir/ritonavir during pregnancy included nine studies involving 2,675 pregnant women. No concerns with the use of these agents were suggested (Pasley 2013).

Nelfinavir

Nelfinavir did not display evidence of teratogenicity in animal experiments. According to the data of the Antiretroviral Pregnancy Registry (2013), the malformation rate is 3.9% (47 of 1,211 births) after first trimester exposure which is a modest evaluation compared to the general population (2.7%). No distinct pattern of birth defects defects has been discovered. In studies with HIV-infected pregnant women it was noted that a small amount crosses the placenta (Bryson 2008, Mirochnick 2002). When nelfinavir is used as an unboosted PI in pregnant women who need treatment for HIV, it is inferior to newer, low-dose ritonavir boosted PIs, but is useful as an alternative PI in combination with 2 NRTIs for the prophylaxis of HIV transmission. However, nevirapine should only be used under special circumstances during pregnancy.

Ritonavir

Ritonavir should be used in combination with other PIs as a low-dose booster to increase levels of a second PI. Only a small amount crosses the placenta (Mirochnick 2002). There is no evidence that ritonavir is teratogenic in animal experiments or humans. According to the data of the Antiretroviral Pregnancy Registry (2013) the malformation rate is 2.3% (52 of 2,260 births) after first trimester exposure, thus similar to the general US population.

Saquinavir

Saquinavir has not demonstrated evidence of teratogenicity in animal experiments or human experience. Like with other PIs only small amounts of the drug cross the placenta (Mirochnick 2002). Pharmacokinetic studies indicate that the newer tablet formulation that has replaced the former capsule formulation, leads to plasma concentrations similar to nonpregnant patients (van der Lugt 2009). Thus, it is not necessary to adjust the doses in pregnancy. Seven birth defects among 182 first trimester exposures were reported to the Antiretroviral Pregnancy Registry (2013). These data are insufficient for a differentiated risk assessment.

Tipranavir

Tipranavir shows no teratogenicity in animal experiments. There are no data about its ability to cross the placenta. Aside from single case reports of pregnant patients with multiple resistances (Weizsaecker 2011, Wensing 2006), there are no other data about the use of tipranavir in pregnancy. No birth defects were reported to the Antiretroviral Pregnancy Registry (2013) among four first trimester exposures to tipranavir. Experiences are insufficient to analyze a possible risk in pregnancy.

2.6.33 Entry inhibitors

Entry inhibitors are antiretroviral agents that inhibit viral binding or fusion of HIV to the cell, either by inhibition of the fusion of the viral capsule with the cell membrane or by blocking CD4- or co-receptors. Data about the use of *enfuvirtide* or *maravorioc* during pregnancy are insufficient to recommend their use during pregnancy (OARAC 2012).

Enfuvirtide

In animal experiments no evidence was observed that *enfuvirtide* is teratogenic. A number of single case reports suggest that enfuvirtide apparently does not cross the placenta (Weizsaecker 2011, Brennan-Benson 2006). According to the data of the Antiretroviral Pregnancy Registry (2013) no birth defects have been reported among 20 first trimester exposure to enfuvirtide. Thus, it can be assumed that the risk of fetal toxicity is likely to be small. Enfuvirtide may be used in pregnant women with multi-resistent HIV in combination with other potent agents as a therapeutic option, but current experience in pregnancy is very limited.

Maraviroc

Maraviroc is a CCR5 inhibitor that is used to treat pretreated HIV-infected adults in combination with other antiretroviral medications, when exclusively CCR5-tropic HIV type-1 have been proven to be present. Animal experiments using rats and rabbits did not show evidence of teratogenicity for maraviroc. There are no data indicating to what degree

maraviroc crosses the placenta. While there has been no indication that the use of maraviroc leads to a higher rate of malignancy, a theoretical concern remains based on the method of its action. Maraviroc should only be used when the benefit justifies the potential fetal risk. There is a lack of data about its application in pregnancy. Among 13 cases with first trimester exposure reported to the Antiretroviral Pregnancy Registry (2013) no birth defects have been observed.

2.6.34 Integrase inhibitors

Integrase inhibitors block integrase, a HIV-coded enzyme, and thereby HIV replication. The use of *raltegravir* during pregnancy can be considered in special circumstances when preferred and alternative agents cannot be used (OARAC 2012). There is insufficient data for the new integrase inhibitors *dolutegravir* and *elvitegravir*.

▶ Dolutegravir

In animal experiments no evidence was seen that *dolutegravir* is teratogenic. Placental transfer has been described in animals. No experiences have been reported about its use during human pregnancy. There are also no reports about the use of dolutegravir to the Antiretroviral Pregnancy Registry (2013).

▶ Elvitegravir

Elvitegravir is combined with *colbicistat* which has no known antiretroviral activity. Colbicistat is a pharmacokinetic enhancer which inhibits enzymes that metabolize elvitegravir. Animal studies of elvitegravir have shown no evidence of teratogenicity. Only one report about the use of elvitagravir during the first trimester has been reported to the Antiretroviral Pregnancy Registry (2013). No birth defects were observed in this case.

▶ Raltegravir

Development studies in rats and rabbits did not show *raltegravir* to be teratogenic. However, there was a slightly increased incidence of supernumerary ribs in the offspring of rats that had received raltegravir at doses about 4.4 times higher than those recommended in human treatment. Potential human risks are not known at this time. According to the few data about its use during pregnancy, raltegravir crosses the placenta well (McKeown 2010). In a case series of five women raltegravir was well tolerated (Taylor 2011). Three birth defects were observed among 141 pregnant women with first trimester exposures reported to the Antiretroviral Pregnancy Registry (2013). Because experience is increasing, the United States guidelines recommend allowing a regimen including raltegravir in special circumstances, when preferred and alternative agents cannot be used (OARAC 2012). However, the data on the use of raltegravir during pregnancy allow no differentiated risk analysis.

2.6.35 Hyperthermia

More than 30 years ago animal experiments demonstrated that an increase in the body temperature can cause malformations (review by Graham 2005, Edwards 1995, Miller 2013). This problem has also been discussed for humans. Neural tube defects, in particular (Suarez 2004, Shaw 1998), but also kidney, heart and abdominal wall defects (Abe 2003, Chambers 1998), have been reported in association with febrile infections in early pregnancy, even though the overall malformation risk is absent or only mildly increased. Moretti (2005) performed a meta-analysis about the risk of neural tube defects and hyperthermia. They included 15 studies with 1,719 cases and found a significant correlation (OR 1.9; 95%; CI 1.61–2.29), both in the nine case-control studies and the six cohort studies. Lowering fever in pregnant women seems to reduce the risk (Suarez 2004).

It has been debated if the use of sauna, electric blankets, or other factors that bring about a short-term increase in body temperature could lead to similar effects as high fever (Suarez 2004). In Finland, where this issue had been investigated repeatedly, visits to saunas occur frequently during pregnancy and is considered safe. The use of electric blankets and heated water beds has not shown, in other investigations, that they are linked to an increased malformation risk.

One study observed that children between the ages of 5 and 12 had more frequent emotional and cognitive deficits where there were reports about high fever during the second and third trimester (Dombrowski 2003).

In summary, it appears that there is a slightly higher risk of malformations when high fever (>39°C and >24 hours) occurs, especially during the first 4 weeks after conception.

Recommendation. If there is an infection with high fever, especially during early pregnancy, the fever should be controlled with acetaminophen (paracetamol) or ibuprofen (Chapter 2.1). Ibuprofen should not be taken after 28 gestational weeks. Non pharmacological measures of fever control such as cool wrappings, and sufficient fluid intake should also be considered. In cases of high fever episodes in early pregnancy, a detailed ultrasound examination should be offered to ascertain the normal development of the fetus. A fever episode does not justify a risk-based termination of pregnancy (Chapter 1.15). Visits to a sauna should be limited to less than 10 minutes, and hot or long baths need to be avoided as well as other sources that can overheat the body.

2.6.36 Long-distance travel and flights

During long-distance travel and flights during pregnancy, a number of potential risks need to be considered:

- Prevention of infections (malaria prophylaxis, see Section 2.6.16.; vaccinations, see Chapter 2.7).
- The risk of other infections (fever, fluid loss), and required therapy.
- During long-distance flights:
  - risks of thrombosis
  - ionizing cosmic radiation

  - decrease of the partial oxygen pressure equivalent to an altitude of 2,500 m
  - dry air.
- Physical and psychological stress.

Specific developmental anomalies have not been found in pregnant women undergoing vaccinations or recommended malaria prophylaxis, nor were such problems seen as a result of long-distance flights.

However, it needs to be noted that the stress of a long-distance trip, especially in predisposed women, might increase the risk of miscarriage. Also, aside from typical infectious diseases, "common" infections may be more prevalent due to altered hygienic standards in the destination country. The accompanying dehydration, fever, or other complications may also endanger the fetus.

The dose of cosmic radiation on a long-distance flight varies markedly – depending on solar activity. Yet, according to current knowledge, no doses are reached that are high enough to lead to an increased risk of malformations.

Recommendation. The need for long distance travel, especially to tropical destinations, by pregnant women should be critically evaluated. Women with a history of miscarriage should preferably postpone their journey. A well-tolerated long-distance journey is no indication to expand prenatal diagnostic interventions.

References

Abdelrahim II, Adam I, Elghazali G et al. Pharmacokinetics of quinine and its metabolites in pregnant Sudanese women with uncomplicated Plasmodium falciparum malaria. J Clin Pharm Ther 2007; 32: 15–19.

Abe K, Honein MA, Moore CA. Maternal febrile illnesses, medication use, and the risk of congenital renal anomalies. Birth Defects Res A Clin Mol Teratol 2003; 67: 911–8.

Adam I, Elwasila el T, Homeida M. Is praziquantel therapy safe during pregnancy? Trans R Soc Trop Med Hyg 2004a; 98: 540–3.

Adam I, Elhassan EM, Omer EM et al. Safety of artemisinins during early pregnancy, assessed in 62 Sudanese women. Ann Trop Med Parasitol 2009; 103: 205–10.

Adam I, Idris HM, Elbashir MI. Quinine for chloroquine-resistant falciparum malaria in pregnant Sudanese women in the first trimester. East Mediterr Health J 2004b; 10: 560–5.

Adam I, Tarning J, Lindegardh N et al. Pharmacokinetics of piperaquine in pregnant women in Sudan with uncomplicated Plasmodium falciparum malaria. Am J Trop Med Hyg 2012; 87: 35–40.

Aksamija A, Horvat G, Habek D et al. Nitrofurantoin-induced acute liver damage in pregnancy. Arh Hig Rada Toksikol 2009; 60: 357–61.

Aleck KA, Bartley DL. Multiple malformation syndrome following fluconazole use in pregnancy: report of an additional patient. Am J Med Genet 1997; 72: 253–6.

Amado JA, Pesquera C, Gonzalez EM et al. Successful treatment with ketoconazole of Cushing's syndrome in pregnancy. Postgrad Med J 1990; 66: 221–3.

Andersen JT, Petersen M, Jimenez-Solem E et al. Clarithromycin in early pregnancy and the risk of miscarriage and malformation: a register based nationwide cohort study. PloS One 2013a; 8: e53327.

Andersen JT, Petersen M, Jimenez-Solem E et al. Trimethoprim use in early pregnancy and the risk of miscarriage: a register-based nationwide cohort study. Epidemiol Infect 2013b; 141: 1749–55.

Andersen JT, Petersen M, Jimenez-Solem E et al. Trimethoprim Use prior to Pregnancy and the Risk of Congenital Malformation: A Register-Based Nationwide Cohort Study. Obstet Gynecol Int 2013c: 364526.

Andrews WW, Sibai BM, Thom EA et al. Randomized clinical trial of metronidazole plus erythromycin to prevent spontaneous preterm delivery in fetal fibronectin-positive women. Obstet Gynecol 2003; 101: 847–55.

Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 through 31 July 2013. Wilmington, NC: Registry Coordinating Center 2013. Available from URL: www.APRegistry.com (accessed on 20–3–2014).

Atmar RL, Englund JA, Hammill H. Complications of measles during pregnancy. Clin Infect Dis 1992; 14: 217–26.

Bahat Dinur A, Koren G, Matok I et al. Fetal safety of macrolides. Antimicrob Agents Chemother 2013; 57: 3307–11.

Bar-Oz B, Diav-Citrin O, Shechtman S et al. Pregnancy outcome after gestational exposure to the new macrolides: a prospective multi-center observational study. Eur J Obstet Gynecol Reprod Biol 2008; 141: 31–4.

Bar-Oz B, Moretti ME, Bishai R et al. Pregnancy outcome after in utero exposure to itraconazole: a prospective cohort study. Am J Obstet Gynecol 2000; 183: 617–20.

Bar-Oz B, Moretti ME, Boskovic R et al. The safety of quinolones – a meta-analysis of pregnancy outcomes. Eur J Obstet Gynecol Reprod Biol 2009; 143: 75–8.

Bar-Oz B, Weber-Schoendorfer C, Berlin M et al. The outcomes of pregnancy in women exposed to the new macrolides in the first trimester: a prospective, multicentre, observational study. Drug Saf 2012; 35: 589–98.

Bardaji A, Sigauque B, Sanz S et al. Impact of malaria at the end of pregnancy on infant mortality and morbidity. J Infect Dis 2011; 203: 691–9.

Bayrak O, Cimentepe E, Inegol I et al. Is single-dose fosfomycin trometamol a good alternative for asymptomatic bacteriuria in the second trimesterof pregnancy? Int Urogynecol J Pelvic Floor Dysfunct 2007; 18: 525–9.

Beard CM, Noller KL, O'Fallon WM et al. Cancer after exposure to metronidazole. Mayo Clin Proc 1988; 63: 147–53.

Beau AB, Hurault-Delarue C, Vial T et al. Safety of oseltamivir during pregnancy: a comparative study using the EFEMERIS database. BJOG 2014; doi: 10.1111/1471-0528.12617 [Epub ahead of print].

Beigi RH, Han K, Venkataramanan R et al. Pharmacokinetics of oseltamivir among pregnant and nonpregnant women. Am J Obstet Gynecol 2011; 204: S84–S88.

Ben David S, Einarson T, Ben DY et al. The safety of nitrofurantoin during the first trimester of pregnancy: meta-analysis. Fundam Clin Pharmacol 1995; 9: 503–7.

Benaboud S, Ekouevi DK, Urien S et al. Population pharmacokinetics of nevirapine in HIV-1-infected pregnant women and their neonates. Antimicrob Agents Chemother 2011; 55: 331–7.

Benhammou V, Tardieu M, Warszawski J et al. Clinical mitochondrial dysfunction in uninfected children born to HIV-infected mothers following perinatal exposure to nucleoside analogues. Environ Mol Mutagen 2007; 48: 173–8.

Berkovitch M, Diav-Citrin O, Greenberg R et al. First-trimester exposure to amoxycillin/clavulanic acid: a prospective, controlled study. Br J Clin Pharmacol 2004; 58: 298–302.

Berkovitch M, Pastuszak A, Gazarian M et al. Safety of the new quinolones in pregnancy. Obstet Gynecol 1994; 84: 535–8.

Berkovitch M, Segal-Socher I, Greenberg R et al. First trimester exposure to cefuroxime: a prospective cohort study. Br J Clin Pharmacol 2000; 50: 161–5.

Berwaerts J, Verhelst J, Mahler C et al. Cushing's syndrome in pregnancy treated by ketoconazole: case report and review of the literature. Gynecol Endocrinol 1999; 13: 175–82.

Best BM, Stek AM, Mirochnick M et al. Lopinavir tablet pharmacokinetics with an increased dose during pregnancy. J Acquir Immune Defic Syndr 2010; 54: 381–8.

Bhargava P, Kuldeep CM, Mathur NK. Antileprosy drugs, pregnancy and fetal outcome. Int J Lepr Other Mycobact Dis 1996; 64: 457–8.

Blanche S, Tardieu M, Rustin P et al. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. Lancet 1999; 354: 1084–9.

Blumberg HM, Burman WJ, Chaisson RE et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am J Respir Crit Care Med 2003; 167: 603–62.

Boronat M, Marrero D, Lopez-Plasencia Y et al. Successful outcome of pregnancy in a patient with Cushing's disease under treatment with ketoconazole during the first trimester of gestation. Gynecol Endocrinol 2011; 27: 675–7.

Bothamley G. Drug treatment for tuberculosis during pregnancy: safety considerations. Drug Saf 2001; 24: 553–65.

Bounyasong S. Randomized trial of artesunate and mefloquine in comparison with quinine sulfate to treat P. falciparum malaria pregnant women. J Med AssocThai 2001; 84: 1289–99.

Brennan-Benson P, Pakianathan M, Rice P et al. Enfurvitide prevents vertical transmission of multidrug-resistant HIV-1 in pregnancy but does not cross the placenta. AIDS 2006; 20: 297–9.
Bristol-Myers Squibb Company. Healthcare Provider Important Drug Warning Letter. 2001. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm173947.htm (accessed on 20-3-2014).
Bruel H, Guillemant V, Saladin-Thiron C et al. Hemolytic anemia in a newborn after maternal treatment with nitrofurantoin at the end of pregnancy. Arch Pediatr 2000; 7: 745–7.
Bryson YJ, Mirochnick M, Stek A et al. Pharmacokinetics and safety of nelfinavir when used in combination with zidovudine and lamivudine in HIV-infected pregnant women: Pediatric AIDS Clinical Trials Group (PACTG) Protocol 353. HIV Clin Trials 2008; 9: 115–25.
Campomori A, Bonati M. Fluconazole treatment for vulvovaginal candidiasis during pregnancy. Ann Pharmacother 1997; 31: 118–9.
Cespedes MS, Castor D, Ford SL et al. Steady-state pharmacokinetics, cord blood concentrations, and safety of ritonavir-boosted fosamprenavir in pregnancy. J Acquir Immune Defic Syndr 2013; 62: 550–4.
Chambers CD, Johnson KA, Dick LM et al. Maternal fever and birth outcome: a prospective study. Teratology 1998; 58: 251–7.
Chappuy H, Treluyer JM, Jullien V et al. Maternal-fetal transfer and amniotic fluid accumulation of nucleoside analogue reverse transcriptase inhibitors in human immunodeficiency virus-infected pregnant women. Antimicrob Agents Chemother 2004; 48: 4332–6.
Chen JY, Ribaudo HJ, Souda S et al. Highly active antiretroviral therapy and adverse birth outcomes among HIV-infected women in Botswana. J Infect Dis 2012; 206: 1695–705.
Chippaux JP, Gardon-Wendel N, Gardon J et al. Absence of any adverse effect of inadvertent ivermectin treatment during pregnancy. Trans R Soc Trop Med Hyg 1993; 87: 318.
Choi JS, Han JY, Ahn HK et al. Fetal outcome after exposure to antihelminthics albendazole and flubendazole during early pregnancy {Abstract}. Birth Defects Res A Clin Mol Teratol 2005; 73: 349.
Choi JS, Han JY, Ahn HK et al. Fetal outcome after exposure to flubendazole during pregnancy {Abstract}. Birth Defects Res A Clin Mol Teratol 2008; 82: 381.
Christian P, Khatry SK, West KP Jr. Antenatal anthelmintic treatment, birthweight, and infant survival in rural Nepal. Lancet 2004; 364: 981–3.
Chun JY, Han JY, Ahn HK et al. Fetal outcome following roxithromycin exposure in early pregnancy. J Matern Fetal Neonatal Med 2006; 19: 189–192.
Clark RL. Embryotoxicity of the artemisinin antimalarials and potential consequences for use in women in the first trimester. Reprod Toxicol 2009; 28: 285–96.
Colbers A, Gingelmaier A, van der Ende M et al. Pharmacokinetics, safety and transplacental passage of rilpivirine in pregnancy: two cases. AIDS 2014; 28: 288–90.
Connor EM, Sperling RS, Gelber R et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. N Engl J Med 1994; 331: 1173–80.
Conway N, Birt BD. Streptomycin in pregnancy: effect on the foetal ear. Br Med J 1965; 2: 260–3.
Cooper WO, Ray WA, Griffin MR. Prenatal prescription of macrolide antibiotics and infantile hypertrophic pyloric stenosis. Obstet Gynecol 2002; 100: 101–6.
Cooper WO, Hernandez-Diaz S, Arbogast PG et al. Antibiotics potentially used in response to bioterrorism and the risk of major congenital malformations. Paediatr Perinat Epidemiol 2009; 23: 18–28.
Costa ML, Souza JP, Oliveira Neto AF et al. Cryptococcal meningitis in HIV negative pregnant women: case report and review of literature. Rev Inst Med Trop Sao Paulo 2009; 51: 289–94.
Cotter AM, Garcia AG, Duthely ML et al. Is antiretroviral therapy during pregnancy associated with an increased risk of preterm delivery, low birth weight, or stillbirth? J Infect Dis 2006; 193: 1195–201.
Cowden J, Hotez P. Mebendazole and albendazole treatment of geohelminth infections in children and pregnant women. Pediatr Infect Dis J 2000; 19: 659–60.
Crider KS, Cleves MA, Reefhuis J et al. Antibacterial medication use during pregnancy and risk of birth defects: National Birth Defects Prevention Study. Arch Pediatr Adolesc Med 2009; 163: 978–5.
Culnane M, Fowler M, Lee SS et al. Lack of long-term effects of in utero exposure to zidovudine among uninfected children born to HIV-infected women. Pediatric AIDS Clinical Trials Group Protocol 219/076 Teams. JAMA 1999; 281: 151–7.

Czeizel A. A case-control analysis of the teratogenic effects of co-trimoxazole. Reprod Toxicol 1990; 4: 305–13.
Czeizel AE, Rockenbauer M. Teratogenic study of doxycycline. Obstet Gynecol 1997; 89: 524–8.
Czeizel AE, Rockenbauer M. A population based case-control teratologic study of oral metronidazole treatment during pregnancy. Br J Obstet Gynaecol 1998; 105: 322–7.
Czeizel AE, Rockenbauer M, Sorensen HT et al. A population-based case-control teratologic study of oral erythromycin treatment during pregnancy. Reprod Toxicol 1999a; 13: 531–6.
Czeizel AE, Toth M, Rockenbauer M. No teratogenic effect after clotrimazole therapy during pregnancy. Epidemiology 1999b; 10: 437–40.
Czeizel AE, Rockenbauer M, Olsen J et al. Oral phenoxymethylpenicillin treatment during pregnancy. Results of a population-based Hungarian case-control study. Arch Gynecol Obstet 2000a; 263: 178–181.
Czeizel AE, Rockenbauer M, Olsen J et al. A case-control teratological study of spiramycin, roxithromycin, oleandomycin and josamycin. Acta Obstet Gynecol Scand 2000b; 79: 234–7.
Czeizel AE, Rockenbauer M, Sorensen HT et al. A teratological study of lincosamides. Scand J Infect Dis 2000c; 32: 579–580.
Czeizel AE, Rockenbauer M. A population-based case-control teratologic study of oral oxytetracycline treatment during pregnancy. Eur J Obstet Gynecol Reprod Biol 2000d; 88: 27–33.
Czeizel AE, Rockenbauer M, Olsen J et al. A teratological study of aminoglycoside antibiotic treatment during pregnancy. Scand J Infect Dis 2000e; 32: 309–13.
Czeizel AE, Rockenbauer M, Sorensen HT et al. A population-based case-control teratologic study of oral chloramphenicol treatment during pregnancy. Eur J Epidemiol 2000f; 16: 323–7.
Czeizel AE, Rockenbauer M, Sorensen HT et al. Augmentin treatment during pregnancy and the prevalence of congenital abnormalities: a population-based case-control teratologic study. Eur J Obstet Gynecol Reprod Biol 2001a; 97: 188–92.
Czeizel AE, Rockenbauer M, Sorensen HT et al. Use of cephalosporins during pregnancy and in the presence of congenital abnormalities: a population-based, case-control study. Am J Obstet Gynecol 2001b; 184: 1289–96.
Czeizel AE, Rockenbauer M, Sorensen HT et al. The teratogenic risk of trimethoprim-sulfonamides: a population based case-control study. Reprod Toxicol 2001c; 15: 637–46.
Czeizel AE, Rockenbauer M, Sorensen HT et al. Nitrofurantoin and congenital abnormalities. Eur J Obstet Gynecol Reprod Biol 2001d; 95: 119–26.
Czeizel AE, Rockenbauer M, Olsen J et al. A population-based case-control study of the safety of oral anti-tuberculosis drug treatment during pregnancy. Int J Tuberc Lung Dis 2001e; 5: 564–8.
Czeizel AE, Kazy Z, Vargha P. A population-based case-control teratological study of vaginal econazole treatment during pregnancy. Eur J Obstet Gynecol Reprod Biol 2003a; 111: 135–40.
Czeizel AE, Kazy Z, Puho E. A population-based case-control teratological study of oral nystatin treatment during pregnancy. Scand J Infect Dis 2003b; 35: 830–5.
Czeizel AE, Kazy Z, Vargha P. A case-control teratological study of vaginal natamycin treatment during pregnancy. Reprod Toxicol 2003c; 17: 387–91.
Czeizel AE, Fladung B, Vargha P. Preterm birth reduction after clotrimazole treatment during pregnancy. Eur J Obstet Gynecol Reprod Biol 2004a; 116: 157–63.
Czeizel AE, Kazy Z, Puho E. Population-based case-control teratologic study of topical miconazole. Congenit Anom (Kyoto) 2004b; 44: 41–5.
Czeizel AE, Metneki J, Kazy Z et al. A population-based case-control study of oral griseofulvin treatment during pregnancy. Acta Obstet Gynecol Scand 2004c; 83: 827–31.
Czeizel AE, Kazy Z, Puho E. Tolnaftate spray treatment during pregnancy. Reprod Toxicol 2004d; 18: 443–4.
de Silva NR, Sirisena JL, Gunasekera DP et al. Effect of mebendazole therapy during pregnancy on birth outcome. Lancet 1999; 353: 1145–9.
de Santis M, Carducci B, De Santis L et al. Periconceptional exposure to efavirenz and neural tube defects. Arch Intern Med 2002; 162: 355.
De Santis M, Di Gianantonio E, Cesari E et al. First-trimester itraconazole exposure and pregnancy outcome: a prospective cohort study of women contacting teratology information services in Italy. Drug Saf 2009; 32: 239–44.

Dean JL, Wolf JE, Ranzini AC et al. Use of amphotericin B during pregnancy: case report and review. Clin Infect Dis 1994; 18: 364–8.
Deen JL, von Seidlein L, Pinder M et al. The safety of the combination artesunate and pyrimethamine-sulfadoxine given during pregnancy. Trans R Soc Trop Med Hyg 2001; 95: 424–8.
Dencker BB, Larsen H, Jensen ES et al. Birth outcome of 1886 pregnancies after exposure to phenoxymethylpenicillin in utero. Clin Microbiol Infect 2002; 8: 196–201.
Deng M, Zhou X, Gao S et al. The effects of telbivudine in late pregnancy to prevent intrauterine transmission of the hepatitis B virus: a systematic review and meta-analysis. Virol J 2012; 9: 185.
Diav-Citrin O, Shechtman S, Arnon J et al. Pregnancy outcome after gestational exposure to mebendazole: a prospective controlled cohort study. Am J Obstet Gynecol 2003; 188: 282–5.
Diav-Citrin O, Shechtman S, Gotteiner T et al. Pregnancy outcome after gestational exposure to metronidazole: a prospective controlled cohort study. Teratology 2001; 63: 186–92.
Dobias L, Cerna M, Rossner P et al. Genotoxicity and carcinogenicity of metronidazole. Mutat Res 1994; 317: 177–94.
Dombrowski SC, Martin RP, Huttunen MO. Association between maternal fever and psychological/behavior outcomes: a hypothesis. Birth Defects Res A Clin Mol Teratol 2003; 67: 905–10.
Donner B, Niranjan V, Hoffmann G. Safety of oseltamivir in pregnancy: a review of preclinical and clinical data. Drug Saf 2010; 33: 631–42.
Drinkard CR, Shatin D, Clouse J. Postmarketing surveillance of medications and pregnancy outcomes: clarithromycin and birth malformations. Pharmacoepidemiol Drug Saf 2000; 9: 549–56.
Drobac PC, del Castillo H, Sweetland A et al. Treatment of multidrug-resistant tuberculosis during pregnancy: long-term follow-up of 6 children with intrauterine exposure to second-line agents. Clin Infect Dis 2005; 40: 1689–92.
Dryden-Peterson S, Shapiro RL, Hughes MD et al. Increased risk of severe infant anemia after exposure to maternal HAART, Botswana. J Acquir Immune Defic Syndr 2011; 56: 428–36.
Dunstan H, Mill A, Stephens S et al. Pregnancy outcome following maternal use of zanamivir or oseltamivir during the 2009 influenza A/H1N1 pandemic: a national prospective surveillance study. BJOG 2014; doi: 10.1111/1471-0528.12640 [Epub ahead of print].
EACS: European AIDS Clinical Society. Europeans Guidelines for treatment of HIV-infected adults in Europe, version 7.0. 2013. Available from URL: www.eacsociety.org (accessed on 20-3-2014).
Edwards MJ, Shiota K, Smith MS et al. Hyperthermia and birth defects. Reprod Toxicol 1995; 9: 411–25.
Ehsanipoor RM, Chung JH, Clock CA et al. A retrospective review of ampicillin-sulbactam and amoxicillin + clavulanate vs cefazolin/cephalexin and erythromycin in the setting of preterm premature rupture of membranes: maternal and neonatal outcomes. Am J Obstet Gynecol 2008; 198: e54–e56.
Einarson A, Phillips E, Mawji F et al. A prospective controlled multicentre study of clarithromycin in pregnancy. Am J Perinatol 1998; 15: 523–5.
Elbadawi NE, Mohamed MI, Dawod OY et al. Effect of quinine therapy on plasma glucose and plasma insulin levels in pregnant women infected with Plasmodium falciparum malaria in Gezira state. East Mediterr Health J 2011; 17: 697–700.
Ely EW, Peacock JE Jr, Haponik EF et al. Cryptococcal pneumonia complicating pregnancy. Medicine (Baltimore) 1998; 77: 153–67.
ECS: European Collaborative Study. Exposure to antiretroviral therapy in utero or early life: the health of uninfected children born to HIV-infected women. J Acquir Immune Defic Syndr 2003; 32: 380–7.
Falagas ME, Vouloumanou EK, Togias AG et al. Fosfomycin versus other antibiotics for the treatment of cystitis: a meta-analysis of randomized controlled trials. J Antimicrob Chemother 2010; 65: 1862–77.
Feiterna-Sperling C, Weizsaecker K, Buhrer C et al. Hematologic effects of maternal antiretroviral therapy and transmission prophylaxis in HIV-1-exposed uninfected newborn infants. J Acquir Immune Defic Syndr 2007; 45: 43–51.
Floridia M, Mastroiacovo P, Tamburrini E et al. Birth defects in a national cohort of pregnant women with HIV infection in Italy, 2001–2011. BJOG 2013; 120: 1466–75.
Flynn PM, Mirochnick M, Shapiro DE et al. Pharmacokinetics and safety of single-dose tenofovir disoproxil fumarate and emtricitabine in HIV-1-infected pregnant women and their infants. Antimicrob Agents Chemother 2011; 55: 5914–22.

Ford N, Calmy A, Mofenson L. Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. AIDS 2011; 25: 2301–04.
Ford N, Mofenson L, Kranzer K et al. Safety of efavirenz in first-trimester of pregnancy: a systematic review and meta-analysis of outcomes from observational cohorts. AIDS 2010; 24: 1461–70.
Fundaro C, Genovese O, Rendeli C et al. Myelomeningocele in a child with intrauterine exposure to efavirenz. AIDS 2002; 16: 299–300.
Furco A, Gosrani B, Nicholas S et al. Successful use of darunavir, etravirine, enfuvirtide and tenofovir/emtricitabine in pregnant woman with multiclass HIV resistance. AIDS 2009; 23: 434–5.
Gardner JS, Guyard-Boileau B, Alderman BW et al. Maternal exposure to prescription and non-prescription pharmaceuticals or drugs of abuse and risk of craniosynostosis. Int J Epidemiol 1998; 27: 64–7.
Gibb DM, Kizito H, Russell EC et al. Pregnancy and infant outcomes among HIV-infected women taking long-term ART with and without tenofovir in the DART trial. PloS Med 2012; 9: e1001217.
Gingelmaier A, Kurowski M, Kastner R et al. Placental transfer and pharmacokinetics of lopinavir and other protease inhibitors in combination with nevirapine at delivery. AIDS 2006; 20: 1737–43.
Glaxo Wellcome. Acyclovir pregnancy registry and valacyclovir pregnancy registry: Interim report for 1 June 1984 through 31 December 1997, Glaxo Wellcome Research Triangle Park, NC USA 1997.
Goldberg O, Koren G, Landau D et al. Exposure to nitrofurantoin during the first trimester of pregnancy and the risk for major malformations. J Clin Pharmacol 2013; 53: 991–5.
Gough AW, Kasali OB, Sigler RE et al. Quinolone arthropathy – acute toxicity to immature articular cartilage. Toxicol Pathol 1992; 20: 436–49.
Graham JM Jr. Marshall J. Edwards: discoverer of maternal hyperthermia as a human teratogen. Birth Defects Res A Clin Mol Teratol 2005; 73: 857–64.
Green MD, van Eijk AM, van Ter Kuile FO et al. Pharmacokinetics of sulfadoxine-pyrimethamine in HIV-infected and uninfected pregnant women in Western Kenya. J Infect Dis 2007; 196: 1403–08.
Greer LG, Leff RD, Rogers VL et al. Pharmacokinetics of oseltamivir according to trimester of pregnancy. Am J Obstet Gynecol 2011; 204: S89–S93.
Greer LG, Sheffield JS, Rogers VL et al. Maternal and neonatal outcomes after antepartum treatment of influenza with antiviral medications. Obstet Gynecol 2010; 115: 711–6.
Guay LA, Musoke P, Fleming T et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. Lancet 1999; 354: 795–802.
Gyapong JO, Chinbuah MA, Gyapong M. Inadvertent exposure of pregnant women to ivermectin and albendazole during mass drug administration for lymphatic filariasis. Trop Med Int Health 2003; 8: 1093–1101.
Gyorkos TW, Larocque R, Casapia M et al. Lack of risk of adverse birth outcomes after deworming in pregnant women. Pediatr Infect Dis J 2006; 25: 791–4.
Han GR, Cao MK, Zhao W et al. A prospective and open-label study for the efficacy and safety of telbivudine in pregnancy for the prevention of perinatal transmission of hepatitis B virus infection. J Hepatol 2011; 55: 1215–21.
Hanson IC, Antonelli TA, Sperling RS et al. Lack of tumors in infants with perinatal HIV-1 exposure and fetal/neonatal exposure to zidovudine. J Acquir Immune Defic Syndr Hum Retrovirol 1999; 20: 463–7.
Heikkilä A, Erkkola R. Review of beta-lactam antibiotics in pregnancy. The need for adjustment of dosage schedules. Clin Pharmacokinet 1994; 27: 49–62.
Heikkilä A, Renkonen OV, Erkkola R. Pharmacokinetics and transplacental passage of imipenem during pregnancy. Antimicrob Agents Chemother 1992; 36: 2652–5.
Hernandez-Diaz S, Werler MM, Walker AM et al. Folic acid antagonists during pregnancy and the risk of birth defects. N Engl J Med 2000; 343: 1608–14.
Hirt D, Urien S, Ekouevi DK et al. Population pharmacokinetics of tenofovir in HIV-1-infected pregnant women and their neonates (ANRS 12109). Clin Pharmacol Ther 2009a; 85: 182–9.
Hirt D, Urien S, Rey E et al. Population pharmacokinetics of emtricitabine in human immunodeficiency virus type 1-infected pregnant women and their neonates. Antimicrob Agents Chemother 2009b; 53: 1067–73.

Hofer H, Donnerer J, Sator K et al. Seminal fluid ribavirin level and functional semen parameters in patients with chronic hepatitis C on antiviral combination therapy. J Hepatol 2010; 52: 812–6.
Hoglund RM, Adam I, Hanpithakpong W et al. A population pharmacokinetic model of piperaquine in pregnant and non-pregnant women with uncomplicated Plasmodium falciparum malaria in Sudan. Malar J 2012; 11: 398.
Hulton SA, Kaplan BS. Renal dysplasia associated with in utero exposure to gentamicin and corticosteroids. Am J Med Genet 1995; 58: 91–3.
Inman W, Pearce G, Wilton L. Safety of fluconazole in the treatment of vaginal candidiasis. A prescription-event monitoring study, with special reference to the outcome of pregnancy. Eur J Clin Pharmacol 1994; 46: 115–8.
Ivanovic J, Bellagamba R, Nicastri E et al. Use of darunavir/ritonavir once daily in treatment-naive pregnant woman: pharmacokinetics, compartmental exposure, efficacy and safety. AIDS 2010; 24: 1083–4.
Jaworsky D, Thompson C, Yudin MH et al. Use of newer antiretroviral agents, darunavir and etravirine with or without raltegravir, in pregnancy: a report of two cases. Antivir Ther 2010; 15: 677–80.
Jepsen P, Skriver MV, Floyd A et al. A population-based study of maternal use of amoxicillin and pregnancy outcome in Denmark. Br J Clin Pharmacol 2003; 55: 216–21.
Jick SS. Pregnancy outcomes after maternal exposure to fluconazole. Pharmacotherapy 1999; 19: 221–2.
Joao EC, Calvet GA, Krauss MR et al. Maternal antiretroviral use during pregnancy and infant congenital anomalies: the NISDI perinatal study. J Acquir Immune Defic Syndr 2010; 53: 176–85.
Joesoef MR, Schmid GP, Hillier SL. Bacterial vaginosis: review of treatment options and potential clinical indications for therapy. Clin Infect Dis 1999; 28: S57–S65.
Jones HC. Intrauterine ototoxicity. A case report and review of literature. J Natl Med Assoc 1973; 65: 201–3, 215.
Kakogawa J, Sakurabashi A, Sadatsuki M et al. Chronic hepatitis B infection in pregnancy illustrated by a case of successful treatment with entecavir. Arch Gynecol Obstet 2011; 284: 1595–6.
Källén BA, Otterblad OP. Maternal drug use in early pregnancy and infant cardiovascular defect. Reprod Toxicol 2003; 17: 255–61.
Källén BA, Otterblad OP, Danielsson BR. Is erythromycin therapy teratogenic in humans? Reprod Toxicol 2005a; 20: 209–14.
Källén BA, Robert-Gnansia E. Maternal drug use, fertility problems, and infant craniostenosis. Cleft Palate Craniofac J 2005b; 42: 589–93.
Källén BA, Danielsson BR. Fetal safety of erythromycin. An update of Swedish data. Eur J Clin Pharmacol 2014; 70: 355–60.
Karunajeewa HA, Salman S, Mueller I et al. Pharmacokinetic properties of sulfadoxine-pyrimethamine in pregnant women. Antimicrob Agents Chemother 2009; 53: 4368–76.
Kazy Z, Puho E, Czeizel AE. Levamisole (Decaris) treatment during pregnancy. Reprod Toxicol 2004; 19: 3.
Kazy Z, Puho E, Czeizel AE. The possible association between the combination of vaginal metronidazole and miconazole treatment and poly-syndactyly population-based case-control teratologic study. Reprod Toxicol 2005a; 20: 89–94.
Kazy Z, Puho E, Czeizel AE. Parenteral polymyxin B treatment during pregnancy. Reprod Toxicol 2005b; 20: 181–2.
Kazy Z, Puho E, Czeizel AE. Population-based case-control study of oral ketoconazole treatment for birth outcomes. Congenit Anom (Kyoto) 2005c; 45: 5–8.
Kenyon SL, Taylor DJ, Tarnow-Mordi W. Broad-spectrum antibiotics for preterm, prelabour rupture of fetal membranes: the ORACLE I randomised trial. ORACLE Collaborative Group. Lancet 2001; 357: 979–88.
King CT, Rogers PD, Cleary JD et al. Antifungal therapy during pregnancy. Clin Infect Dis 1998; 27: 1151–60.
Kirkwood A, Harris C, Timar N et al. Is gentamicin ototoxic to the fetus? J Obstet Gynaecol Can 2007; 29: 140–5.
Klarskov P, Andersen JT, Jimenez-Solem E et al. Short-acting sulfonamides near term and neonatal jaundice. Obstet Gynecol 2013; 122: 105–10.
Klebanoff MA, Carey JC, Hauth JC et al. Failure of metronidazole to prevent preterm delivery among pregnant women with asymptomatic Trichomonas vaginalis infection. N Engl J Med 2001; 345: 487–93.

Knapp KM, Brogly SB, Muenz DG et al. Prevalence of congenital anomalies in infants with in utero exposure to antiretrovirals. Pediatr Infect Dis J 2012; 31: 164–70.
Knudsen LB. No association between griseofulvin and conjoined twinning. Lancet 1987; 2: 1097.
Knudtson E, Para M, Boswell H et al. Drug rash with eosinophilia and systemic symptoms syndrome and renal toxicity with a nevirapine-containing regimen in a pregnant patient with human immunodeficiency virus. Obstet Gynecol 2003; 101: 1094–7.
Koss CA, Baras DC, Lane SD et al. Investigation of metronidazole use during pregnancy and adverse birth outcomes. Antimicrob Agents Chemother 2012; 56: 4800–05.
Kourtis AP, Schmid CH, Jamieson DJ et al. Use of antiretroviral therapy in pregnant HIV-infected women and the risk of premature delivery: a meta-analysis. AIDS 2007; 21: 6 07–15.
Laiprasert J, Klein K, Mueller BA et al. Transplacental passage of vancomycin in noninfected term pregnant women. Obstet Gynecol 2007; 109: 1105–10.
Larsen B, Glover DD. Serum erythromycin levels in pregnancy. Clin Ther 1998; 20: 971–7.
Larsen H, Nielsen GL, Schonheyder HC et al. Birth outcome following maternal use of fluoroquinolones. Int J Antimicrob Agents 2001; 18: 259–62.
Le Chenadec J, Mayaux MJ, Guihenneuc-Jouyaux C et al. Perinatal antiretroviral treatment and hematopoiesis in HIV-uninfected infants. AIDS 2003; 17: 2053–61.
Lee SJ, McGready R, Fernandez C et al. Chloroquine pharmacokinetics in pregnant and nonpregnant women with vivax malaria. Eur J Clin Pharmacol 2008; 64: 987–92.
Lessnau KD, Qarah S. Multidrug-resistant tuberculosis in pregnancy: case report and review of the literature. Chest 2003; 123: 953–6.
Lewis JH. Drug hepatotoxicity in pregnancy. Eur J Gastroenterol Hepatol 1991; 3: 883–91.
Lin HC, Lin HC, Chen SF. Increased risk of low birthweight and small for gestational age infants among women with tuberculosis. BJOG 2010; 117: 585–90.
Lin KJ, Mitchell AA, Yau WP et al. Maternal exposure to amoxicillin and the risk of oral clefts. Epidemiology 2012; 23: 699–705.
Lin KJ, Mitchell AA, Yau WP et al. Safety of macrolides during pregnancy. Am J Obstet Gynecol 2013; 208: 221–8.
Linder N, Amarilla M, Hernandez A et al. Association of high-dose bifonazole administration during early pregnancy and severe limb reduction defects in the newborn. Birth Defects Res A Clin Mol Teratol 2010; 88: 201–4.
Liu M, Cai H, Yi W. Safety of telbivudine treatment for chronic hepatitis B for the entire pregnancy. J Viral Hepat 2013; 20: 65–70.
Loebstein R, Addis A, Ho E et al. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. Antimicrob Agents Chemother 1998; 42: 1336–9.
Lopez-Rangel E, Van Allen MI. Prenatal exposure to fluconazole: an identifiable dysmorphic phenotype. Birth Defects Res A Clin Mol Teratol 2005; 73: 919–23.
Louik C, Werler MM, Mitchell AA. Erythromycin use during pregnancy in relation to pyloric stenosis. Am J Obstet Gynecol 2002; 186: 288–90.
Lowe CR. Congenital defects among children born to women under supervision or treatment for pulmonary tuberculosis. Br J Prev Soc Med 1964; 18: 14–16.
Lush R, Iland H, Peat B et al. Successful use of dapsone in refractory pregnancy-associated idiopathic thrombocytopenic purpura. Aust NZ J Med 2000; 30: 105–7.
Mahon BE, Rosenman MB, Kleiman MB. Maternal and infant use of erythromycin and other macrolide antibiotics as risk factors for infantile hypertrophic pyloric stenosis. J Pediatr 2001; 139: 380–4.
Malm H, Artama M, Gissler M et al. First trimester use of macrolides and risk of major malformations {OTIS Abstract}. Birth Defects Res Part A Clin Mol Teratol 2008; 82: 412.
Mandelbrot L, Kermarrec N, Marcollet A et al. Case report: nucleoside analogue-induced lactic acidosis in the third trimester of pregnancy. AIDS 2003; 17: 272–3.
Mandelbrot L, Landreau-Mascaro A, Rekacewicz C et al. Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1. JAMA 2001; 285: 2083–93.
Manka W, Solowiow R, Okrzeja D. Assessment of infant development during an 18-month follow-up after treatment of infections in pregnant women with cefuroxime axetil. Drug Saf 2000; 22: 83–8.
Manyando C, Mkandawire R, Puma L et al. Safety of artemether-lumefantrine in pregnant women with malaria: results of a prospective cohort study in Zambia. Malar J 2010; 9: 249.
Martorell C, Theroux E, Bermudez A et al. Safety and efficacy of fosamprenavir in human immunodeficiency virus-infected pregnant women. Pediatr Infect Dis J 2010; 29: 985.

Marzolini C, Rudin C, Decosterd LA et al. Transplacental passage of protease inhibitors at delivery. AIDS 2002; 16: 889–93.
Mastroiacovo P, Mazzone T, Botto LD et al. Prospective assessment of pregnancy outcomes after first-trimester exposure to fluconazole. Am J Obstet Gynecol 1996; 175: 1645–50.
McClure EM, Goldenberg RL, Dent AE et al. A systematic review of the impact of malaria prevention in pregnancy on low birth weight and maternal anemia. Int J Gynaecol Obstet 2013; 121: 103–9.
McCormack WM, George H, Donner A et al. Hepatotoxicity of erythromycin estolate during pregnancy. Antimicrob Agents Chemother 1977; 12: 630–5.
McElhatton P, Stephens S. Preliminary data on exposure to mebendazole during pregnancy {Abstract}. Reprod Toxicol 2007; 24: 62.
McGready R, Ashley EA, Moo E et al. A randomized comparison of artesunate-atovaquone-proguanil versus quinine in treatment for uncomplicated falciparum malaria during pregnancy. J Infect Dis 2005; 192: 846–53.
McGready R, Brockman A, Cho T et al. Randomized comparison of mefloquine-artesunate versus quinine in the treatment of multidrug-resistant falciparum malaria in pregnancy. Trans R Soc Trop Med Hyg 2000; 94: 689–93.
McGready R, Cho T, Keo NK et al. Artemisinin antimalarials in pregnancy: a prospective treatment study of 539 episodes of multidrug-resistant Plasmodium falciparum. Clin Infect Dis 2001; 33: 2009–16.
McGready R, Stepniewska K, Edstein MD et al. The pharmacokinetics of atovaquone and proguanil in pregnant women with acute falciparum malaria. Eur J Clin Pharmacol 2003; 59: 545–52.
McGready R, Tan SO, Ashley EA et al. A randomised controlled trial of artemether-lumefantrine versus artesunate for uncomplicated plasmodium falciparum treatment in pregnancy. PLoS Med 2008; 5: e253.
McGready R, Thwai KL, Cho T et al. The effects of quinine and chloroquine antimalarial treatments in the first trimester of pregnancy. Trans R Soc Trop Med Hyg 2002; 96: 180–4.
McKeown DA, Rosenvinge M, Donaghy S et al. High neonatal concentrations of raltegravir following transplacental transfer in HIV-1 positive pregnant women. AIDS 2010; 24: 2416–8.
McNellis D, McLeod M, Lawson J et al. Treatment of vulvovaginal candidiasis in pregnancy. A comparative study. Obstet Gynecol 1977; 50: 674–8.
Mercieri M, Di RR, Pantosti A et al. Critical pneumonia complicating early-stage pregnancy. Anesth Analg 2010; 110: 852–4.
Metneki J, Czeizel A. Griseofulvin teratology. Lancet 1987; 1: 1042.
Mickal A, Panzer JD. The safety of lincomycin in pregnancy. Am J Obstet Gynecol 1975; 121: 1071–4.
Miller MW, Church CC. Arrhenius thermodynamics and birth defects: chemical teratogen synergy. Untested, testable, and projected relevance. Birth Defects Res C 2013; 99: 50–60.
Mirochnick M, Fenton T, Gagnier P et al. Pharmacokinetics of nevirapine in human immunodeficiency virus type 1-infected pregnant women and their neonates. Pediatric AIDS Clinical Trials Group Protocol 250 Team. J Infect Dis 1998; 178: 368–74.
Mirochnick M, Best BM, Stek AM et al. Atazanavir pharmacokinetics with and without tenofovir during pregnancy. J Acquir Immune Defic Syndr 2011; 56: 412–9.
Mirochnick M, Dorenbaum A, Holland D et al. Concentrations of protease inhibitors in cord blood after in utero exposure. Pediatr Infect Dis J 2002; 21: 835–8.
Mohamed A, Dresser GK, Mehta S. Acute respiratory failure during pregnancy: a case of nitrofurantoin-induced pneumonitis. CMAJ 2007; 176: 319–20.
Mølgaard-Nielsen D, Hviid A. Maternal use of antibiotics and the risk of orofacial clefts: a nationwide cohort study. Pharmacoepidemiol Drug Saf 2012; 21: 246–53.
Mølgaard-Nielsen D, Pasternak B, Hviid A. Use of oral fluconazole during pregnancy and the risk of birth defects. N Engl J Med 2013; 369: 830–9.
Moretti ME, Bar-Oz B, Fried S et al. Maternal hyperthermia and the risk for neural tube defects in offspring: systematic review and meta-analysis. Epidemiology 2005; 16: 216–9.
Morris CA, Onyamboko MA, Capparelli E et al. Population pharmacokinetics of artesunate and dihydroartemisinin in pregnant and non-pregnant women with malaria. Malar J 2011; 10: 114.
Mosha D, Mazuguni F, Mrema S et al. Safety of artemether-lumefantrine exposue in first trimester of pregnancy: an observational cohort. Malar J 2014; 13: 197.
Mpairwe H, Webb EL, Muhangi L et al. Anthelminthic treatment during pregnancy is associated with increased risk of infantile eczema: randomized-controlled trial results. Pediatr Allergy Immunol 2011; 22: 305–12.

Mueller M, Balasegaram M, Koummuki Y et al. A comparison of liposomal amphotericin B with sodium stibogluconate for the treatment of visceral leishmaniasis in pregnancy in Sudan. J Antimicrob Chemother 2006; 58: 811–5.

Muller AE, Dorr PJ, Mouton JW et al. The influence of labour on the pharmacokinetics of intravenously administered amoxicillin in pregnant women. Br J Clin Pharmacol 2008; 66: 866–74.

Myles TD, Elam G, Park-Hwang E et al. The Jarisch-Herxheimer reaction and fetal monitoring changes in pregnant women treated for syphilis. Obstet Gynecol 1998; 92: 859–64.

Na-Bangchang K, Manyando C, Ruengweerayut R et al. The pharmacokinetics and pharmacodynamics of atovaquone and proguanil for the treatment of uncomplicated falciparum malaria in third-trimester pregnant women. Eur J Clin Pharmacol 2005; 61: 573–82.

Nanovskaya T, Patrikeeva S, Zhan Y et al. Transplacental transfer of vancomycin and telavancin. Am J Obstet Gynecol 2012; 207: 331–6.

Ndibazza J, Muhangi L, Akishule D et al. Effects of deworming during pregnancy on maternal and perinatal outcomes in Entebbe, Uganda: a randomized controlled trial. Clin Infect Dis 2010; 50: 531–40.

Ndyomugyenyi R, Kabatereine N, Olsen A et al. Efficacy of ivermectin and albendazole alone and in combination for treatment of soil-transmitted helminths in pregnancy and adverse events: a randomized open label controlled intervention trial in Masindi district, western Uganda. Am J Trop Med Hyg 2008; 79: 856–63.

Neou P, Gyftodemou Y, Valti E et al. Famciclovir exposure during organogenesis {Abstract}. Reprod Toxicol 2004; 18: 742.

Newman RD, Parise ME, Slutsker L et al. Safety, efficacy and determinants of effectiveness of antimalarial drugs during pregnancy: implications for prevention programmes in Plasmodium falciparum-endemic sub-Saharan Africa. Trop Med Int Health 2003; 8: 488–506.

Nordeng H, Lupattelli A, Romoren M et al. Neonatal outcomes after gestational exposure to nitrofurantoin. Obstet Gynecol 2013; 121: 306–13.

Nørgaard M, Pedersen L, Gislum M et al. Maternal use of fluconazole and risk of congenital malformations: a Danish population-based cohort study. J Antimicrob Chemother 2008; 62: 172–6.

Nørgård B, Czeizel AE, Rockenbauer M et al. Population-based case control study of the safety of sulfasalazine use during pregnancy. Aliment Pharmacol Ther 2001; 15: 483–6.

Nosten F, Vincenti M, Simpson J et al. The effects of mefloquine treatment in pregnancy. Clin Infect Dis 1999; 28: 808–15.

Nyunt MM, Adam I, Kayentao K et al. Pharmacokinetics of sulfadoxine and pyrimethamine in intermittent preventive treatment of malaria in pregnancy. Clin Pharmacol Ther 2010; 87: 226–34.

OARAC (Working group of the office of AIDS research advisory council), Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. 2012. Available from URL: http://aidsinfo.nih.gov/guidelines (accessed on 20–3–2014).

Osadchy A, Ratnapalan T, Koren G. Ocular toxicity in children exposed in utero to antimalarial drugs: review of the literature. J Rheumatol 2011; 38: 2504–08.

Ouyang DW, Brogly SB, Lu M et al. Lack of increased hepatotoxicity in HIV-infected pregnant women receiving nevirapine compared with other antiretrovirals. AIDS 2010; 24: 109–14.

Ouyang DW, Shapiro DE, Lu M et al. Increased risk of hepatotoxicity in HIV-infected pregnant women receiving antiretroviral therapy independent of nevirapine exposure. AIDS 2009; 23: 2425–30.

Ozyüncü O, Beksac MS, Nemutlu E et al. Maternal blood and amniotic fluid levels of moxifloxacin, levofloxacin and cefixime. J Obstet Gynaecol Res 2010; 36: 484–7.

Pacifici GM. Transfer of antivirals across the human placenta. Early Hum Dev 2005; 81: 647–54.

Pacque M, Munoz B, Poetschke G et al. Pregnancy outcome after inadvertent ivermectin treatment during community-based distribution. Lancet 1990; 336: 1486–9.

Padberg S, Wacker E, Meister R et al. Observational Cohort Study of Pregnancy Outcome after First-Trimester Exposure to Fluoroquinolones. Antimicrob. Agents Chemother 2014; 58: 4392–98.

Pagliano P, Carannante N, Rossi M et al. Visceral leishmaniasis in pregnancy: a case series and a systematic review of the literature. J Antimicrob Chemother 2005; 55: 229–33.
Pan CQ, Duan ZP, Bhamidimarri KR et al. An algorithm for risk assessment and intervention of mother to child transmission of hepatitis B virus. Clin Gastroenterol Hepatol 2012; 10: 452–9.
Paparone PW, Menghetti RA. Case report: neurocysticercosis in pregnancy. NJ Med 1996; 93: 91–4.
Pasley MV, Martinez M, Hermes A et al. Safety and efficacy of lopinavir/ritonavir during pregnancy: a systematic review. AIDS Rev 2013; 15: 38–48.
Pasternak B, Hviid A. Use of acyclovir, valacyclovir, and famciclovir in the first trimester of pregnancy and the risk of birth defects. JAMA 2010; 304: 859–66.
Pasternak B, Hviid A. Atovaquone-proguanil use in early pregnancy and the risk of birth defects. Arch Intern Med 2011; 171: 259–60.
Patel K, Shapiro DE, Brogly SB et al. Prenatal protease inhibitor use and risk of preterm birth among HIV-infected women initiating antiretroviral drugs during pregnancy. J Infect Dis 2010; 201: 1035–44.
Pescovitz MD. Absence of teratogenicity of oral ganciclovir used during early pregnancy in a liver transplant recipient. Transplantation 1999; 67: 758–9.
Phillips-Howard PA, Wood D. The safety of antimalarial drugs in pregnancy. Drug Saf 1996; 14: 131–45.
Phiri K, Hernandez-Diaz S, Dugan KB et al. First Trimester Exposure to Antiretroviral Therapy and Risk of Birth Defects. Pediatr Infect Dis J 2014 [Epub ahead of print].
Pinnetti C, Tamburrini E, Ragazzoni E et al. Decreased plasma levels of darunavir/ritonavir in a vertically infected pregnant woman carrying multiclass-resistant HIV type-1. Antivir Ther 2010; 15: 127–9.
Piola P, Nabasumba C, Turyakira E et al. Efficacy and safety of artemether-lumefantrine compared with quinine in pregnant women with uncomplicated Plasmodium falciparum malaria: an open-label, randomised, non-inferiority trial. Lancet Infect Dis 2010; 10: 762–9.
Pipitone MA, Gloster HM. A case of blastomycosis in pregnancy. J Am Acad Dermatol 2005; 53: 740–1.
Poespoprodjo JR, Fobia W, Kenangalem E, Lampah DA, Sugiarto P, Tjitra E, Anstey NM, and Price RN. Dihydroartemisinin-piperaquine treatment of multidrug resistant falciparum and vivax malaria in pregnancy. PLoS One 2014; 9: e84976
Puhó EH, Szunyogh M, Metneki J et al. Drug treatment during pregnancy and isolated orofacial clefts in Hungary. Cleft Palate Craniofac J 2007; 44: 194–202.
Puliyanda DP, Silverman NS, Lehman D et al. Successful use of oral ganciclovir for the treatment of intrauterine cytomegalovirus infection in a renal allograft recipient. Transpl Infect Dis 2005; 7: 71–4.
Pursley TJ, Blomquist IK, Abraham J et al. Fluconazole-induced congenital anomalies in three infants. Clin Infect Dis 1996; 22: 336–40.
Reyes MP, Ostrea EM Jr, Cabinian AE et al. Vancomycin during pregnancy: does it cause hearing loss or nephrotoxicity in the infant? Am J Obstet Gynecol 1989; 161: 977–81.
Rezvani M, Koren G. Pregnancy outcome after exposure to injectable ribavirin during embryogenesis. Reprod Toxicol 2006; 21: 113–5.
Ripamonti D, Cattaneo D, Maggiolo F et al. Atazanavir plus low-dose ritonavir in pregnancy: pharmacokinetics and placental transfer. AIDS 2007; 21: 2409–15.
Roberts SS, Miller RK, Jones JK et al. The Ribavirin Pregnancy Registry: Findings after 5 years of enrollment, 2003–2009. Birth Defects Res A Clin Mol Teratol 2010; 88: 551–9.
Robinson GC, Cambon KG. Hearing loss in infants of tuberculous mothers treated with streptomycin during pregnancy. N Engl J Med 1964; 271: 949–51.
Romøren M, Lindbaek M, Nordeng H. Pregnancy outcome after gestational exposure to erythromycin – a population-based register study from Norway. Br J Clin Pharmacol 2012; 74: 1053–62.
Rosa FW, Hernandez C, Carlo WA. Griseofulvin teratology, including two thoracopagus conjoined twins. Lancet 1987; 1: 171.
Rubin A, Dvornik D. Placental transfer of griseofulvin. Am J Obstet Gynecol 1965; 92: 882–3.
Saito S, Minakami H, Nakai A et al. Outcomes of infants exposed to oseltamivir or zanamivir in utero during pandemic (H1N1) 2009. Am J Obstet Gynecol 2013; 209: 130–9.

Sánchez Sainz-Trápaga C, Gutierrez FR, Ibanez RC et al. Relationship between a case of severe hearing loss and use of gentamycin in the pregnant mother. An Esp Pediatr 1998; 49: 397–8.
Santos F, Sheehy O, Perreault S et al. Exposure to anti-infective drugs during pregnancy and the risk of small-for-gestational-age newborns: a case-control study. BJOG 2011; 118: 1374–82.
Sarkar MS, Rowland K, Koren G. Pregnancy outcome following gestational exposure to terbinafine: A prospective comparative study [OTIS Abstract]. Birth Defects Res A Clin Mol Teratol 2003; 67: 390.
Sarkar M, Woodland C, Koren G et al. Pregnancy outcome following gestational exposure to azithromycin. BMC Pregnancy Childbirth 2006; 6: 18.
Sarner L, Fakoya A. Acute onset lactic acidosis and pancreatitis in the third trimester of pregnancy in HIV-1 positive women taking antiretroviral medication. Sex Transm Infect 2002; 78: 58–9.
Schaefer C, Amoura-Elefant E, Vial T et al. Pregnancy outcome after prenatal quinolone exposure. Evaluation of a case registry of the European Network of Teratology Information Services (ENTIS). Eur J Obstet Gynecol Reprod Biol 1996; 69: 83–9.
Schardein JL. Chemically Induced Birth Defects. 4th ed. Marcel Dekker, New York, Basel 2000.
Schlagenhauf P, Blumentals WA, Suter P et al. Pregnancy and fetal outcomes after exposure to mefloquine in the pre- and periconception period and during pregnancy. Clin Infect Dis 2012; 54: e124–31.
Schmid C, Kuemmerle A, Blum J et al. In-hospital safety in field conditions of nifurtimox eflornithine combination therapy (NECT) for T.B. gambiense sleeping sickness. PLoS Negl Trop Dis 2012; 6: e1920.
Shaw GM, Todoroff K, Velie EM et al. Maternal illness, including fever and medication use as risk factors for neural tube defects. Teratology 1998; 57: 1–7.
Shea K, Hilburger E, Baroco A et al. Successful treatment of vancomycin-resistant Enterococcus faecium pyelonephritis with daptomycin during pregnancy. Ann Pharmacother 2008; 42: 722–5.
Shennan A, Crawshaw S, Briley A et al. A randomised controlled trial of metronidazole for the prevention of preterm birth in women positive for cervicovaginal fetal fibronectin: the PREMET Study. BJOG 2006; 113: 65–74.
Shin S, Guerra D, Rich M et al. Treatment of multidrug-resistant tuberculosis during pregnancy: a report of 7 cases. Clin Infect Dis 2003; 36: 996–1003.
Shoai Tehrani M, Sicre de Fontbrune F, Roth P et al. Case report of exposure to voriconazole in the second and third trimesters of pregnancy. Antimicrob Agents Chemother 2013; 57: 1094–5.
Shulman CE, Dorman EK. Importance and prevention of malaria in pregnancy. Trans R Soc Trop Med Hyg 2003; 97: 30–5.
Simon A, Warszawski J, Kariyawasam D et al. Association of prenatal and postnatal exposure to lopinavir-ritonavir and adrenal dysfunction among uninfected infants of HIV-infected mothers. JAMA 2011; 306: 70–8.
Sørensen HT, Nielsen GL, Olesen C et al. Risk of malformations and other outcomes in children exposed to fluconazole in utero. Br J Clin Pharmacol 1999; 48: 234–8.
Sperling RS, Shapiro DE, McSherry GD et al. Safety of the maternal-infant zidovudine regimen utilized in the Pediatric AIDS Clinical Trial Group 076 Study. AIDS 1998; 12: 1805–13.
Stek AM, Best BM, Luo W et al. Effect of pregnancy on emtricitabine pharmacokinetics. HIV Med 2012; 13: 226–35.
Stone KM, Reiff-Eldridge R, White AD et al. Pregnancy outcomes following systemic prenatal acyclovir exposure: Conclusions from the international acyclovir pregnancy registry, 1984–1999. Birth Defects Res A Clin Mol Teratol 2004; 70: 201–7.
Stroup JS, Wagner J, Badzinski T. Use of daptomycin in a pregnant patient with Staphylococcus aureus endocarditis. Ann Pharmacother 2010; 44: 746–9.
Suarez L, Felkner M, Hendricks K. The effect of fever, febrile illnesses, and heat exposures on the risk of neural tube defects in a Texas-Mexico border population. Birth Defects Res A Clin Mol Teratol 2004; 70: 815–9.
Svensson T, Granath F, Stephansson O et al. Birth outcomes among women exposed to neuraminidase inhibitors during pregnancy. Pharmacoepidemiol Drug Saf 2011; 20: 1030–4.

Tagbor H, Bruce J, Browne E et al. Efficacy, safety, and tolerability of amodiaquine plus sulphadoxine-pyrimethamine used alone or in combination for malaria treatment in pregnancy: a randomised trial. Lancet 2006; 368: 1349–56.
Tanaka T, Nakajima K, Murashima A et al. Safety of neuraminidase inhibitors against novel influenza A (H1N1) in pregnant and breastfeeding women. CMAJ 2009; 181: 55–8.
Tarantal AF, Castillo A, Ekert JE et al. Fetal and maternal outcome after administration of tenofovir to gravid rhesus monkeys (Macaca mulatta). J Acquir Immune Defic Syndr 2002; 29: 207–20.
Tarning J, Kloprogge F, Dhorda M et al. Pharmacokinetic properties of artemether, dihydroartemisinin, lumefantrine, and quinine in pregnant women with uncomplicated plasmodium falciparum malaria in Uganda. Antimicrob Agents Chemother 2013; 57: 5096–103.
Tarning J, McGready R, Lindegardh N et al. Population pharmacokinetics of lumefantrine in pregnant women treated with artemether-lumefantrine for uncomplicated Plasmodium falciparum malaria. Antimicrob Agents Chemothem 2009; 53: 3837–46.
Taylor AW, Mosimaneotsile B, Mathebula U et al. Pregnancy outcomes in HIV-infected women receiving long-term isoniazid prophylaxis for tuberculosis and antiretroviral therapy. Infect Dis Obstet Gynecol 2013: 195637.
Taylor GP, Clayden P, Dhar J et al. British HIV Association guidelines for the management of HIV infection in pregnant women 2012. HIV Med 2012; 13: 87–157.
Taylor N, Touzeau V, Geit M et al. Raltegravir in pregnancy: a case series presentation. Int J STD AIDS 2011; 22: 358–60.
Thomas F, Erhart A, D'Alessandro U. Can amodiaquine be used safely during pregnancy? Lancet Infect Dis 2004; 4: 235–9.
Torp-Pedersen A, Jimenez-Solem E, Andersen JT et al. Exposure to mebendazole and pyrvinium during pregnancy: a Danish nationwide cohort study. Infect Dis Obstet Gynecol 2012: 769851.
Townsend CL, Cortina-Borja M, Peckham CS et al. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000–2006. AIDS 2008; 22: 973–81.
Tuomala RE, Watts DH, Li D et al. Improved obstetric outcomes and few maternal toxicities are associated with antiretroviral therapy, including highly active antiretroviral therapy during pregnancy. J Acquir Immune Defic Syndr 2005; 38: 449–73.
Ugwumadu A, Manyonda I, Reid F et al. Effect of early oral clindamycin on late miscarriage and preterm delivery in asymptomatic women with abnormal vaginal flora and bacterial vaginosis: a randomised controlled trial. Lancet 2003; 361: 983–8.
van der Lugt J, Colbers A, Molto J et al. The pharmacokinetics, safety and efficacy of boosted saquinavir tablets in HIV type-1-infected pregnant women. Antivir Ther 2009; 14: 443–50.
Vinther Skriver M, Nørgaard M, Pedersen L et al. Pivmecillinam and adverse birth and neonatal outcomes: a population-based cohort study. Scand J Infect Dis 2004; 36: 733–7.
Wade NA, Unadkat JD, Huang S et al. Pharmacokinetics and safety of stavudine in HIV-infected pregnant women and their infants: Pediatric AIDS Clinical Trials Group protocol 332. J Infect Dis 2004; 190: 2167–74.
Wang Y, Livingston E, Patil S et al. Pharmacokinetics of didanosine in antepartum and postpartum human immunodeficiency virus-infected pregnant women and their neonates: an AIDS clinical trials group study. J Infect Dis 1999; 180: 1536–41.
Wang X, Nanovskaya TN, Zhan Y et al. Pharmacokinetics of metronidazole in pregnant patients with bacterial vaginosis. J Matern Fetal Neonatal Med 2011; 24: 444–8.
Warszawski J, Tubiana R, Le CJ et al. Mother-to-child HIV transmission despite antiretroviral therapy in the ANRS French Perinatal Cohort. AIDS 2008; 22: 289–99.
Watts DH, Huang S, Culnane M et al. Birth defects among a cohort of infants born to HIV-infected women on antiretroviral medication. J Perinat Med 2011; 39: 163–70.
Webb EL, Mawa PA, Ndibazza J et al. Effect of single-dose anthelmintic treatment during pregnancy on an infant's response to immunisation and on susceptibility to infectious diseases in infancy: a randomised, double-blind, placebo-controlled trial. Lancet 2011; 377: 52–62.
Weizsaecker K, Kurowski M, Hoffmeister B et al. Pharmacokinetic profile in late pregnancy and cord blood concentration of tipranavir and enfuvirtide. Int J STD AIDS 2011; 22: 294–5.

Wensing AM, Boucher CA, van Kasteren M et al. Prevention of mother-to-child transmission of multi-drug resistant HIV-1 using maternal therapy with both enfuvirtide and tipranavir. AIDS 2006; 20: 1465–7.

WHO. Report of the WHO informal consultation on the use of praziquantel during pregnancy/lactation and albendazole/mebendazole in children under 24 months. Available from: http://whqlibdoc.who.int/hq/2003/WHO_CDS_CPE_PVC_2002.4.pdf, 2002 (accessed on 14-3-2014).

WHO. Assessment of the safety of artemisinin compounds in pregnancy. Report of two joint informal consultations convened in 2006. Available from: http://whqlibdoc.who.int/publications/2007/9789241596114_eng.pdf, 2006 (accessed on 14-3-2014).

WHO. Guidelines for treatment of tuberculosis, 2010a. Available from: http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf?ua=1 (accessed on 12-3-2014).

WHO. Guidelines for the treatment of malaria, 2010b. Available from: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed on 14-3-2014).

WHO. Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: recommendations for a public health approach, 2010c version. Available from: http://whqlibdoc.who.int/publications/2010/9789241599818_eng.pdf (accessed on 14-3-2014).

WHO. Chagas disease (American trypanosomiasis), 2013a. Available from: http://www.who.int/mediacentre/factsheets/fs340/en/index.html (accessed on 12-3-2014).

WHO. Malaria in pregnant women, 2013b. Available from: http://who.int/malaria/areas/high_risk_groups/pregnancy/en (accessed on 12-3-2014).

WHO. Soil-transmitted helminth infections; Factsheet No. 366, 2013c; Updated June 2013. Available from: http://www.who.int/mediacentre/factsheets/fs366/en"http://www.who.int/mediacentre/factsheets/fs366/en (accessed on 17-3-2014).

Wogelius P, Norgaard M, Gislum M et al. Further analysis of the risk of adverse birth outcome after maternal use of fluoroquinolones. Int J Antimicrob Agents 2005; 26: 323–6.

Xie HY, Yasseen AS III, Xie RH et al. Infant outcomes among pregnant women who used oseltamivir for treatment of influenza during the H1N1 epidemic. Am J Obstet Gynecol 2013; 208: 293–7.

Yalaz M, Akisu M, Hilmioglu S et al. Successful caspofungin treatment of multidrug resistant Candida parapsilosis septicaemia in an extremely low birth weight neonate. Mycoses 2006; 49: 242–5.

Yang J, Xie RH, Krewski D et al. Exposure to trimethoprim/sulfamethoxazole but not other FDA category C and D anti-infectives is associated with increased risks of preterm birth and low birth weight. Int J Infect Dis 2011; 15: e336–e341.

Yaris F, Kesim M, Kadioglu M et al. Gentamicin use in pregnancy. A renal anomaly. Saudi Med J 2004; 25: 958–9.