Appendix 1. Risk associated with the use of drugs used to treat opportunistic infections in pregnancy and during breastfeeding

Drug	Briggs pregnancy category	Breastfeeding category	Notes
Aciclovir[a]	Compatible	Compatible	Crosses the placenta. Overall, the data do not suggest an increased risk of congenital malformation or other adverse fetal outcomes from exposure to either systemic aciclovir or topical aciclovir at any time in pregnancy. However, outcomes other than congenital malformation have not been adequately studied to exclude an increased risk
Amphotericin B[b]	Compatible	No human data; probably compatible	No reports linking the use of amphotericin B with congenital defects have been found. Although the animal data suggest risk, no adverse effects have been reported in exposed human embryos and fetuses. The drug crosses the human placenta with cord blood concentrations up to those measured in the mother. Reversible renal damage and hypokalaemia were found in some infants after birth
Anidulafungin	No human data; animal data suggest low risk	No human data; potential toxicity	If required, the benefit probably outweighs the unknown risk. Use the lowest possible dose. Transfer to the fetus might occur
Atovaquone[b]	Compatible; maternal benefit >> risk to embryo/fetus	No human data; potential toxicity	Data suggest that atovaquone may cross the placenta. The use of atovaquone during human pregnancy does not appear to increase the risk of major birth defects. The lack of toxicity in animals with doses close to those used in humans is reassuring. The authors of two reviews [1,2] concluded that the drug could be used in pregnancy. Because the maternal benefit appears to exceed the unknown risk to the embryo/fetus, atovaquone should not be withheld because of pregnancy
Azithromycin[a,b]	Compatible	Compatible	The human pregnancy data do not suggest a risk to the embryo/fetus of developmental toxicity from azithromycin. The antibiotic has not been associated with an increased risk of pyloric stenosis

Drug	Briggs pregnancy category	Breastfeeding category	Notes
Cidofovir[b]	Compatible; maternal benefit >> risk to embryo/fetus	Contraindicated	No reports of use in human pregnancy. Placental transfer to the fetus should be expected. Adverse effects observed at very low doses in animal studies. The molecular weight (about 315) suggests that the drug will be excreted in breast milk
Clarithromycin[a]	Compatible	Compatible	Crosses the placenta. The animal reproduction data suggest a high risk, but the available human pregnancy experience suggests that the risk, if it exists, is low. The antibiotic has not been associated with an increased risk of pyloric stenosis
Clindamycin[b]	Compatible, avoid first trimester if possible	Compatible	Crosses the placenta; fetal blood levels approximately 50% of maternal levels. The published data for first trimester exposure to clindamycin are limited to two studies with different findings on the risk of birth defects [3,4]. Until additional data are available, use during organogenesis should be limited to situations in which there are no alternatives
Dapsone[b]	Compatible; maternal benefit >> risk to embryo/fetus	Limited human data; potential toxicity	Folic acid 5 mg daily or folinic acid 5 mg/week supplements should be given if pyrimethamine is co-prescribed. Probably crosses the placenta but the use of dapsone during pregnancy does not appear to present a major risk to the fetus or the neonate. Monitor closely for blood dyscrasias during use
Ethambutol[b]	Compatible	Limited human data; probably compatible	Crosses the placenta. The literature supports the safety of ethambutol in combination with isoniazid and rifampin during pregnancy. No reports linking the use of ethambutol with congenital defects have been found
Fluconazole[a]	Human data suggest risk (>400 mg/day)	Compatible	Expected to cross the placenta. Limited data but appears teratogenic with continuous use in the first trimester at doses >400 mg daily. Women prescribed >400 mg daily should use effective contraception during treatment and for 1 week after completing high-dose fluconazole treatment. Published experience with use of smaller doses suggests that the risk is low. Avoid use with phenytoin. Placental transfer to the fetus should be expected. In those instances in which continuous, high-dose fluconazole is the only therapeutic option during the first trimester, the mother should be informed of the potential risk to the fetus
Flucytosine[b]	Contraindicated in first trimester	No human data; potential	Amphotericin B is considered to be first-line treatment of choice for susceptible disseminated mycotic infections during pregnancy. Flucytosine is partially (~4%)

Drug	Briggs pregnancy category	Breastfeeding category	Notes
		toxicity	metabolised to 5-fluorouracil which is a known teratogen. Crosses the placenta. Several case reports of second and third trimester exposure with no defects observed
Foscarnet[b]	Compatible; maternal benefit >> risk to embryo/fetus	Contraindicated	Placental transfer to the fetus should be expected. Because of the frequent occurrence of renal toxicity experienced with foscarnet in adults, frequent antepartum testing of the fetus and close monitoring of the amniotic fluid volume to observe for fetal renal toxicity is recommended
Ganciclovir[b]	Compatible; maternal benefit >> risk to embryo/fetus	No human data; potential toxicity	Avoid use in the first trimester if possible; use to prevent or treat fetal infection might be reasonable. No adverse fetal effects reported in four cases in a review in 2017 [5]. Crosses the placenta. Women of reproductive potential should be advised to use effective contraception during therapy and for at least 30 days after the discontinuation of treatment with ganciclovir. Due to its mutagenic potential, men should be advised to practice barrier contraception during and for at least 90 days following treatment with ganciclovir. May cause temporary or permanent female and male infertility
Itraconazole[b]	Human data suggest low risk	Limited human data; potential toxicity	Avoid during organogenesis if possible. Following inadvertent exposure or where itraconazole must be used, the risk to the fetus is low. Placental transfer to the fetus should be expected. The manufacturer advises that women of reproductive potential should use highly effective contraception during and for 2 months following completion of therapy for onychomycosis
Pentamidine[b]	Compatible; maternal benefit >> risk to embryo/fetus	Contraindicated	Concentrates in the placenta with placental transfer following intravenous administration but very low systemic exposure following nebulised therapy
Primaquine	Contraindicated	No human data; potential toxicity	The fetus is relatively G6PD deficient; risk of acute haemolysis regardless of mother's G6PD status. Placental transfer should be expected. Effective contraception should be used by women of childbearing potential during treatment and for the remaining ovulatory cycle after discontinuation and by men during treatment and for 3 months after discontinuation

Drug	Briggs pregnancy category	Breastfeeding category	Notes
Pyrimethamine[b]	Compatible; maternal benefit >> risk to embryo/fetus	Limited human data; probably compatible	Folinic acid 15 mg daily (or folic acid 5 mg daily) recommended to prevent folate deficiency. Crosses the placenta. Some studies recommend avoiding in the first trimester
Rifabutin[b]	No human data; animal data suggest moderate risk	No human data; potential toxicity	Maternal benefit appears to outweigh unknown risk. Placental transfer to the fetus should be expected
Rifampicin[b]	Compatible	Compatible	Prophylactic vitamin K recommended for neonates. Crosses the placenta
Sulfonamides[b]	Human data suggest risk in third trimester	Limited human data; potential toxicity	Potential toxicity to the neonate if used near term (jaundice, haemolytic anaemia and kernicterus). Readily cross the placenta
Trimethoprim[a] (see sulfonamides)	Human and animal data suggest risk	Compatible	Associated with cardiovascular, neural tube and possibly oral cleft defects in some reports but published placebo-controlled trials have failed to demonstrate an increase in fetal abnormalities. Crosses the placenta. Folic acid 400 μg – 5 mg daily before conception or concurrently with trimethoprim may reduce the risk of congenital defects
Valaciclovir	Compatible	Compatible	Human pregnancy data for valaciclovir are extremely limited but do not signal an increased malformation risk; other pregnancy and fetal outcomes have not been assessed. Oral valaciclovir is converted to aciclovir
Valganciclovir[b]	Compatible; maternal benefit >> risk to embryo/fetus	Contraindicated	No reports of use in human pregnancy. Avoid use in the first trimester if possible, but use to prevent or treat fetal infection might be reasonable due to the risk of CMV to the fetus. Crosses the placenta. Oral valganciclovir is converted to ganciclovir. Due to mutagenic and teratogenic potential, women of reproductive potential should be advised to use effective contraception during therapy and for 30 days following treatment. Likewise, men should be advised to use barrier contraception during and for at least 90 days following therapy

Drug	Briggs pregnancy category	Breastfeeding category	Notes
			Valganciclovir at the recommended dose may cause temporary or permanent infertility in women and men
Voriconazole[b]	Limited human data; animal data suggest risk	No human data; potential toxicity	If possible avoid at least in the first trimester. Placental transfer to the fetus should be expected

All agents were checked in August 2023 using all of the following resources (unless otherwise stated): (i) Briggs Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk [4]; (ii) UK Teratology Information Service (UKTIS: https://uktis.org/); and (iii) Best Use of Medicines in Pregnancy (Bumps; https://www.medicinesinpregnancy.org/medicine--pregnancy/).
[a]A Bumps patient information leaflet is produced by UKTIS and is available at www.medicinesinpregnancy.org; [b]not listed in UKTIS/Bumps.
CMV, cytomegalovirus; G6PD, glucose-6-phosphate dehydrogenase.

References

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