

Folic acid supplementation at 0.4 mg/day is routinely recommended for all women of reproductive potential,¹⁵² to reduce the risk of neural tube defects (**AI**). Since neural tube closure occurs early in pregnancy, often before pregnancy is diagnosed, all persons planning a pregnancy or with reproductive potential should take daily folic acid supplementation. There is also evidence that folic acid supplementation may decrease risk of congenital heart defects, cleft lip and palate,¹⁵³ preterm birth,¹⁵⁴ low birth weight, and the fetus being small for gestational age.^{155,156} There are no trials evaluating whether supplementation at higher levels (e.g., 4 mg/day as recommended for pregnant women who previously had an infant with a neural tube defect) would reduce the risk of birth defects associated with first-trimester TMP-SMX use. A multicenter double-blind randomized clinical trial in women of childbearing age who planned pregnancy within 12 months failed to show an advantage of folic acid 4 mg versus 0.4 mg daily on the occurrence of congenital malformations; however, the higher dose was associated with lower occurrence of spontaneous abortion, the fetus being small for gestational age, and preterm delivery.¹⁵⁷ The authors noted that the study was underpowered for the outcome of congenital malformations.¹⁵⁷ Other studies have found that higher doses of folic acid (4–6 mg/day) are associated with less frequent neural tube defects, oral clefts, and recurrent preeclampsia.^{158–160} In a large, population-based, case-control study, the increased odds of congenital cardiovascular anomalies associated with TMP-SMX use in pregnancy were not seen in women also receiving folic acid supplementation, most of whom received folic acid 6 mg/day (OR 1.24; 95% CI, 0.94–1.62).¹⁴⁴

Although the risk of multiple congenital abnormalities associated with TMP-SMX use persisted despite supplemental folic acid, the OR decreased from 6.4 for TMP-SMX without folic acid to 1.9 for TMP-SMX plus folic acid. Based on these findings, with the suggestion of a dose-response effect of folic acid supplementation and the known effects of TMP-SMX as a folic acid antagonist, for women who are on TMP-SMX, clinicians should consider giving them supplemental folic acid 4 mg/day prior to pregnancy if they are capable of becoming pregnant or as soon as possible in the first trimester in those who are pregnant (**BII**). Leucovorin (folinic acid) is an active form of folate and is commonly used to counteract the effect of folic acid antagonists, especially as an adjunct in the treatment of various cancers. However, it is chemically different from folic acid and is not interchangeable. A randomized, controlled trial demonstrated that adding leucovorin to TMP-SMX for the treatment of PCP was associated with an increased risk of therapeutic failure and death.⁹⁵ In addition, there are case reports of failure of TMP-SMX prophylaxis in the setting of concurrent leucovorin use.¹⁶¹ If a higher dose of supplemental folic acid is given, its use should be limited to the first trimester (**AIII**). Whether or not a person receives supplemental folic acid during the first trimester, a follow-up ultrasound is recommended at 18 weeks to 20 weeks to assess fetal anatomy with consideration for subsequent follow-up scans (**BIII**).

Although historically there has been concern about the risk of neonatal kernicterus in the setting of maternal sulfonamide or dapsone use near delivery, reviews have found no cases of kernicterus reported in neonates after maternal ingestion of sulfonamides or with the use of TMP-SMX in neonates.^{162–164} For several decades, dapsone has been used safely to treat leprosy, malaria, and various dermatologic conditions during pregnancy.^{165,166} Long-term therapy is associated with a risk of mild maternal hemolysis, and exposed fetuses with G6PD deficiency are at potential risk (albeit extremely low) of acute hemolytic anemia.¹⁶⁷

Data on atovaquone in human pregnancy are limited but preclinical studies have not demonstrated teratogenicity in rats or rabbits at plasma concentrations corresponding to estimated human exposure during malaria treatment.¹⁶⁸ A systematic review of the safety of atovaquone-proguanil for the prevention and treatment of malaria in pregnancy found miscarriages in 21 of 260 women (8.08%;