Systematic Review of the Safety of Trimethoprim-Sulfamethoxazole for Prophylaxis in HIV-Infected Pregnant Women: Implications for Resource-Limited Settings

Fatu Forna[1,2], Michelle McConnell[3,4], Florence N. Kitabire[5], Jaco Homsy[5], John T. Brooks[2], Jonathan Mermin[4,5] and Paul J. Weidle[2]

[1]Epidemic Intelligence Service, Division of Applied Public Health Training, Epidemiology Program Office, CDC, Atlanta, GA, USA; [2]Division of HIV/AIDS Prevention, National Center for HIV, STD, and TB Prevention (NCHSTP), CDC, Atlanta, GA, USA; [3]Thailand Ministry of Public Health, US CDC Collaboration, Nonthaburi, Thailand; [4]Global AIDS Program, NCHSTP, CDC, Atlanta, GA, USA; [5]Global AIDS Program, CDC-Uganda, Uganda Virus Research Institute, Entebbe, Uganda

Abstract

Daily prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMZ) significantly decreases morbidity and mortality among people living with HIV. Some clinicians are reluctant to use TMP-SMZ in pregnant and breastfeeding HIV-infected women because of concerns about the possible teratogenicity when used in the first trimester and about its potential to induce hyperbilirubinemia near term and during early breastfeeding.

We systematically reviewed evidence regarding the toxicity of TMP-SMZ prophylaxis in pregnant and breastfeeding women to help guide practice in resource-limited settings. We identified relevant literature by searching PubMed and MEDLINE via OVID, Embase, and Science Citation Index for data on hyperbilirubinemia, kernicterus, and teratogenicity associated with administration of sulfonamides and TMP-SMZ through July 2005. We also reviewed the reference lists of identified articles.

Most studies demonstrated that TMP-SMZ was not associated with hyperbilirubinemia when administered to mothers during pregnancy and breastfeeding. No cases of kernicterus were reported in neonates after maternal ingestion of sulfonamides. There is mixed evidence linking ingestion of TMP-SMZ and other sulfonamides in early pregnancy to elevated risks of oral clefts, neural tube defects, and cardiovascular and urinary tract abnormalities, although some sources found that supplementation with folic acid might ameliorate this potential risk. Existing guidelines recommend that HIV-infected pregnant women receive prophylaxis, but they differ with regards to stage of disease at which to initiate treatment, need for CD4+ T-lymphocyte testing, and prophylaxis during the first trimester. Existing data indicate that the risk of serious injury to neonates from maternal use of daily TMP-SMZ prophylaxis during pregnancy and breastfeeding is small. Given the substantial benefits of TMP-SMZ prophylaxis for HIV-infected women living in resource-limited settings, this review indicates that it is safe to abide by the WHO guidelines recommending daily TMP-SMZ prophylaxis for HIV-infected pregnant women. **(AIDS Reviews 2006;8:24-36)**

Key words

Hyperbilirubinemia. Kernicterus. Trimethoprim. Sulfamethoxazole. Sulfonamide. Pregnancy. HIV.

Correspondence to:
Fatu Forna
Centers for Disease Control & Prevention
1600 Clifton Road, MS-E45
Atlanta, GA 30333, USA
E-mail: fforna@cdc.gov

Introduction

Studies of HIV-infected persons in sub-Saharan Africa have demonstrated that daily trimethoprim-sulfamethoxazole (TMP-SMZ) prophylaxis reduces mortality by 20-46%, and decreases incidence of malaria, bacterial pneumonia, and diarrheal illness as well as hospitalizations[1-7]. Over half of all persons living with HIV in the world are female. In developing countries, young women 15-24 years of age comprise 64% of people living with HIV or AIDS[8]. Prior to the widespread use of TMP-SMZ prophylaxis in developed countries, *Pneumocystis jiroveci* pneumonia (PCP) was a major cause of morbidity and mortality among HIV-infected patients. Among HIV-infected pregnant women in the USA, mortality from PCP was 50% and it accounted for 80% of pregnancy associated AIDS deaths[9-10].

TMP-SMZ is classified for use in pregnancy as a category C drug, indicating that it should be used only when the potential benefit exceeds the potential risk[11-12]. Concerns about possible teratogenicity when used in the first trimester and induction of hyperbilirubinemia near term and during early breastfeeding have made some clinicians reluctant to prescribe daily TMP-SMZ prophylaxis for HIV-infected pregnant and breastfeeding women, despite multiple guideline documents recommending its use in this population. This paper is a systematic review of the evidence regarding the toxicity of TMP-SMZ with regards to its use as prophylaxis in pregnant and breastfeeding HIV-infected women.

Methods

We identified relevant literature by searching PubMed and MEDLINE via OVID from 1950 to 2005, Embase from 1980 to 2005, and Science Citation Index from 1980 to 2005. We used the subject headings "trimethoprim-sulfamethoxazole and pregnancy", trimethoprim and pregnancy", "sulfonamide and pregnancy", "sulfonamide and kernicterus", and "sulfonamide and hyperbilirubinemia" to perform the computerized literature search. To ensure completeness, we also reviewed the reference lists of all identified articles. We included only reports that documented the use of TMP-SMZ, trimethoprim, or any sulfonamide in humans during pregnancy, and that reported the clinical outcomes of hyperbilirubinemia, kernicterus, or congenital abnormalities in the infant.

Forty-six reports fit the criteria and were included in the systematic review. Reports included randomized studies, cohort studies, case-control studies, case series, and case reports. Data are presented in the form of a structured summary describing the studies' characteristics and findings and are presented in the tables[13]. A quantitative meta-analysis was not performed because of the heterogeneity of the studies evaluated, the treatments used, and the outcomes examined[13-14].

Characteristics of trimethoprim-sulfamethoxazole

TMP-SMZ is a synthetic antibacterial combination product that blocks two consecutive steps of folate metabolism involved in the biosynthesis of nucleic acids and proteins essential to many bacteria and some parasites[12]. The recommended dose of TMP-SMZ for prophylaxis in HIV-infected adults, including pregnant women, is one double-strength tablet a day (160 mg trimethoprim, 800 mg sulfamethoxazole)[15-16]. TMP-SMZ can be produced generically and is available widely in resource-limited settings for about US $10 per year[17].

Both drugs are excreted in low concentrations in human milk and cross the placental barrier reaching peak fetal levels within three hours after administration[11-12,18]. Fetal levels of sulfamethoxazole and other sulfonamides average 70-90% of maternal levels, and significant levels may persist in the newborn for several days after birth when given near term[12]. Sulfamethoxazole is classified as an intermediate-acting sulfonamide with regard to its rate of absorption and elimination[19]. Labeling information for Septra® (trimethoprim-sulfamethoxazole) states that "Septra® is contraindicated in pregnant and nursing mothers, because sulfonamides pass the placenta and are excreted in the milk and may cause kernicterus", and that "Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, Septra® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus"[11].

Reported incidence of adverse reactions to TMP-SMZ in adults and children may be lower among Africans than among persons living in industrialized nations and consist mostly of skin eruptions[1,2,11,17,20]. Severe adverse reactions can include Stevens-Johnson syndrome, neutropenia, thrombocytopenia, and renal or hepatic insufficiency[11,15,17,21]. TMP-SMZ is contraindicated in patients who have had a severe adverse reaction to the drug or other sulfonamides[11,15]. It is recommended that HIV-infected patients with a non-life-threatening adverse reaction continue the drug for prophylaxis, or have desensitization or reintroduction at a reduced dose or frequency if the drug has been discontinued[22,23]. Individuals with glucose-6-phosphate

Table 1: Altered bilirubin metabolism – Evidence for increased risk

Year	Author	Drug	Report type	Exposure period	Exposed	Number of Infants: With hyperbilirubinemia	With kernicterus	Treatment indication / Notes
1941	Heckel[33]	Sulfanilamide	Case series	Month 3-8	13	1	0	Various "infectious" reasons
1942	Ginzler[34]	Sulfanilamide	Case report	Case 1: during labor Case 2: "shortly before delivery"	2	2	0	Case 1: Chorioamnionitis, infant died 8 days after delivery Case 2: "Infection"
1956	Silverman[35]	Sulfisoxazole	Randomized clinical trial	Drug given directly to neonates	95	Not noted	12	Antibiotic prophylaxis for premature infants; 60/95 infants in penicillin/ sulfisoxazole group died; 27/97 died in oxytetracycline group
1964	Dunn[36]	Sulfamethoxy-pyridazine		Case series 2-84 days after rupture of membranes	9	9	0	Antibiotic prophylaxis after premature rupture of membranes; 6 infants were premature
1965	Brown[37]	Sulfamethoxy-pyridazine	Case report	Case 1: 2 weeks before delivery Case 2: 2 days before	2	2	0	Urinary tract infection; both infants deliverywith glucose-6-phosphate dehydrogenase (G6PD) deficiency
1971	Perkins[38]	Sulfisoxazole	Case report	2 weeks before delivery	1	0	0	Urinary tract infection; G6PD deficient mother; stillborn male infant with anemia and hydrops fetalis

dehydrogenase (G6PD) deficiency are also susceptible to sulfonamide-induced hemolysis, and there is an increased incidence of neonatal hyperbilirubinemia among infants with G6PD deficiency[24,25].

Hyperbilirubinemia and kernicterus

Bilirubin is the end product of heme catabolism, and it is bound mostly to albumin with only a small quantity existing freely in plasma. Sulfonamides have an affinity for albumin and can displace bilirubin, increasing the amount of free bilirubin in the plasma[26]. The glucuronyl transferase system that conjugates most bilirubin for excretion is immature in neonates, especially premature neonates, thus predisposing them to hyperbilirubinemia[27,28]. Kernicterus is a neurologic syndrome that results from deposition of free bilirubin in neuronal tissues of the central nervous system[26,28,29]. Clinical manifestations include loss of the Moro reflex, a weak suck, poor feeding, lethargy, vomiting, a high-pitched cry, fever, seizures, and muscle rigidity[26-28]. Mortality rates of up to 70% have been reported in symptomatic infants, and those who survive usually have serious neurologic sequelae including hearing loss, seizures, and mental deficiency[26-29].

Neonatal hyperbilirubinemia or jaundice, defined as total serum bilirubin exceeding 5 mg/dl, occurs in most infants and is usually benign, but may require treatment with phototherapy or exchange transfusion to prevent kernicterus[30,31]. Hyperbilirubinemia is observed typically in 60% of full term and 80% of preterm infants during the first week of life[28]. Bilirubin concentrations < 20 mg/dl are generally considered safe for full term newborns[26,28]. Most kernicterus occurs in infants with a bilirubin level ≥ 25 mg/dl, although premature infants may develop kernicterus at lower levels[26,28,29]. A 1999 review of laboratory records of more than 50,000 California newborns found that 2% had total serum bilirubin levels > 20 mg/dl; 0.15% > 25 mg/dl; and only 0.01% > 30 mg/dl[32]. As many as a third of infants with untreated hemolytic disease and serum bilirubin levels > 20 mg/dl may develop kernicterus[24].

Altered bilirubin metabolism – Evidence for increased risk

The first case reports describing neonatal hyperbilirubinemia after maternal ingestion of sulfonamides appeared in 1941 and 1942[33,34] (Table 1). A 1956 randomized trial of two prophylactic antibacterial regimens

administered to premature infants demonstrated higher rates of kernicterus and mortality among 95 infants treated with a combination of penicillin and subcutaneous sulfisoxazole compared to 97 infants treated with oxytetracycline[35]. Further concern was raised in 1964 by a report of jaundice in the newborns of nine women who had received daily oral doses of sulphamethoxypyridazine as antibiotic prophylaxis after premature rupture of membranes[36]. The authors noted that sulfonamides, especially long-acting sulfonamides such as sulphamethoxypyridazine, may be dangerous to the newborn and should not be administered to women during pregnancy or to infants during the first week of life. In 1965 maternal ingestion of sulfamethoxypyridazine near term was also reported to cause jaundice in two infants with G6PD deficiency[37]. Finally, a case report in 1971 described the stillbirth of a male fetus born to a G6PD-deficient mother, possibly related to maternal sulfisoxazole ingestion for a urinary tract infection two weeks before delivery[38].

Altered bilirubin metabolism – Evidence for safety

In 1938 two studies reported the cases of 34 women given sulfanilamide during labor and noted no adverse events in their infants[39,40] (Table 2). Another 1938 study of 19 pregnant women treated with a five-day course of sulfanilamide for gonorrhea reported that there were no "harmful effects" on the baby[41]. A 1959 study of 17 women treated with sulfadimethoxine reported no adverse events in their infants[42]. In 1961 a study of 44 mothers given oral sulfisoxazole during labor reported no episodes of hyperbilirubinemia or kernicterus[43]. A 1976 study of 46 women given sulfadimidine during labor also found that bilirubin levels were not significantly altered in their infants[44].

A 1965 review of the clinical records of 100 infants born to mothers with a history of rheumatic fever receiving sulfadiazine prophylaxis throughout their pregnancies, identified seven infants with jaundice that was attributed to "physiologic" reasons (four infants), and blood group incompatibility (three infants); they observed no evidence of kernicterus[45]. The authors concluded that antenatal sulfadiazine prophylaxis was not associated with an increased incidence of prematurity, hyperbilirubinemia, or kernicterus. A later investigation by the same authors in 1980 of an additional 94 infants born to mothers with a history of rheumatic fever receiving sulfadiazine prophylaxis during pregnancy identified nine cases of neonatal jaundice that they attributed to "physiologic" reasons (seven infants), Rhesus incompatibility (one infant), and blood group incompatibility (one infant); again no evidence of kernicterus was observed[46].

A 1979 study of five patients with ulcerative colitis who became pregnant during treatment with oral sulfasalazine and who were maintained on therapy throughout their pregnancies noted that sulfasalazine was present in cord blood and breast milk, but that the use of the drug did not adversely affect their infants[47]. A 1981 study on the placental transfer of sulfasalazine among 11 pregnant women with inflammatory bowel disease who were administered the drug daily reported no adverse events in their infants[48]. In 1981 the same author reported on an additional 12 pregnant women with inflammatory bowel disease who were treated with daily sulfasalazine and noted that their newborn infants were "all healthy"[49]. A 1981 survey of American gastroenterologists evaluating the experience of 174 women who received sulfasalazine and corticosteroids for inflammatory bowel disease throughout their pregnancies, found that none of their infants developed jaundice[50]. A 1981 case series of eight pregnant women treated with sulfasalazine for ulcerative colitis also found that none of their infants developed jaundice[51].

In 1987 a study of 15 infants born to mothers with inflammatory bowel disease who received sulfasalazine during pregnancy and lactation reported no cases of kernicterus and two cases of hyperbilirubinemia, neither of which required treatment[52]. In 1989 a report on the treatment of 43 cases of *Toxoplasma* infection throughout pregnancy with spiramycin, pyrimethamine, and sulfonamides found that "no neonatal complications could be attributed to prenatal treatment with sulfonamides"[53]. In 2003 a Danish report found no association between the use of sulfamethizole late in pregnancy in 40 women and risk of neonatal jaundice[54]. Finally, case-reports have described treatment of PCP in two pregnant women with TMP-SMZ, and treatment of toxoplasmosis in two pregnant women with sulfadiazine[55-58]. The women delivered viable infants who were discharged home within one week of delivery, but no specific information was given about the presence or absence of hyperbilirubinemia.

Congenital abnormalities - Evidence for increased risk

A 1971 case-control study of 458 mothers of infants with congenital abnormalities found an increased risk of congenital anomalies associated with maternal ingestion of sulfonamides throughout pregnancy[59] (Table 3). This study also found an increased risk of congenital abnormalities associated with maternal ingestion of aspi-

Table 2: Altered bilirubin metabolism – Evidence for safety

Year	Author	Drug	Report type	Exposure period	Number of infants: Exposed	With hyperbiliru-binemia	With kernicterus	Treatment indication / Notes
1938	Speert[39]	Sulfanilamide	Pharmaco-kinetic study	During labor	17	0	0	None
1938	Barker[40]	Sulfanilamide	Case series	During labor	17	0	0	"Infectious processes"
1938	Bomze[41]	Sulfanilamide	Clinical trial	Month 3-9	19	0	0	Gonorrhea
1959	Lucey[42]	Sulfadi-methoxine	Pharmaco-kinetic study	During labor	17	0	0	None
1961	Kantor[43]	Sulfisoxazole	Pharmaco-kinetic	During labor	44	0	0	None
1965	Morgan[45]	Sulfadiazine	Cohort study	Throughout pregnancy	100	7	0	Endocarditis prophylaxis
1976	Drew[44]	Sulfadimidine	Cohort study	During labor	46	8	0	Numerous indications
1979	Khan[47]	Sulfasalazine	Case series	Throughout pregnancy	5	0	0	Ulcerative colitis
1980	Baskin[46]	Sulfadiazine	Cohort study	Throughout pregnancy	94	9	0	Endocarditis prophylaxis
1981	Levy[51]	Sulfasalazine	Case series	Trimester 1-3	8	0	0	Ulcerative colitis
1981	Jarnerot[48]	Sulfasalazine	Pharmaco-kinetic study	Trimester 1-3	11	0	0	Inflammatory bowel disease
1981	Jarnerot[49]	Sulfasalazine	Pharmaco-kinetic study	Trimester 1-3	12	0	0	Inflammatory bowel disease
1981	Mogadam[50]	Sulfasalazine	Cohort study	Throughout pregnancy	174	0	0	Inflammatory bowel disease
1987	Esbjorner[52]	Sulfasalazine	Case series	Throughout pregnancy	15	2	0	Inflammatory bowel disease
1989	Hohlfeld[53]	Sulfadoxine or Sulfadiazine	Cohort study	Throughout pregnancy	43	0	0	*Toxoplasma* infection
2003	Ratanajamit[54]	Sulfamethizole	Cohort study	Last 14 days before delivery	40	5	0	Urinary tract infection

rin, antacids, nicotinamide, iron, and other common drugs. A 1975 case-control study of 599 Finnish children with cleft lip reported an association between oral clefts with "additional malformations" and maternal ingestion of sulfonamides in the first and second trimester of pregnancy[60]. Other agents associated with oral clefts in this study included iron, vitamins, salicylates, penicillin, and anticonvulsants.

A 2000 case-control study that included 6932 infants with congenital abnormalities found that consumption of dihydrofolate reductase inhibitors (trimethoprim, triamterene, and sulfasalazine) in the second or third month of pregnancy was associated with increased risk of oral clefts and cardiovascular defects, and that folic acid supplementation might reduce these risks[61]. A 2001 case-control study by the same authors of 1242 infants with neural-tube defects found that trimethoprim was also associated with increased risk of neural-tube defects when taken in the first trimester[62]. In 2001 an evaluation of 22,865 women with newborns or fetuses with congenital abnormalities in the Hungarian Case-Control Surveillance of Congenital Abnormalities Study, found an increased risk of cardiovascular and urinary tract malformations among infants whose mothers ingested TMP-SMZ in the second and third month of pregnancy, and cardiovascular malformations among infants whose mothers ingested trimethoprim-sulfamethazine in the second and third months of pregnancy[63]. A protective effect against the malformations was associated with taking high doses of folic acid (6 mg/d) with TMP-SMZ. An evaluation of 22,843 infants with congenital abnormalities from the same database in 2004 found a higher rate of cardiovascular malformation and clubfoot in infants born to mothers who ingested different sulfonamides in the second and third months of pregnancy[64]. In 2001 a report on a study of 195 HIV-infected women with first trimester exposure to the combination of antiretroviral therapy and folate antagonists also found that exposure to both agents was associated with an increased risk of congenital abnormalities[65].

A 1966 report described limb defects and multiple other abnormalities in an infant whose mother ingested sulfaguanidine during the seventh week of pregnan-

Table 3: Congenital abnormalities – Evidence for increased risk

Year	Author	Drug	Report type	Exposure period	Participants	Main findings
1966	Pogorzelska[66]	Sulfaguanidine	Case report	Week 7	Mother treated with a total of 15 grams for food poisoning	Infant born with multiple abnormalities including "decreased brain size", "limb defects", "heart defects", and a "neck abnormality".
1971	Nelson[59]	Sulfonamides	Case-control study	Throughout pregnancy	458 mothers of infants with major and minor congenital abnormalities; 911 mothers of infants without abnormalities	Higher proportion of mothers of infants with major abnormalities took sulfonamides ($p < 0.05$) – 35/175 (20%) case-mothers versus 114/911 (12.5%) control-mothers
1975	Saxen[60]	Sulfonamides	Case-control study	Trimester 1 and 2	599 Finnish children with cleft lip, cleft palate, and oral clefts with "additional malformations" and their matched controls	Higher proportion of mothers of infants with oral clefts and "additional malformations" took sulfonamides ($p < 0.05$) – First trimester: 11/134 (8.2%) case-mothers versus 39/599 (6.5%) control-mothers; Second trimester: 10/134 (7.5%) case-mothers versus 27/599 (4.5%) control-mothers
1980	Craxi[67]	Sulfasalazine	Case report	Throughout pregnancy	Mother with ulcerative colitis receiving daily sulfasalazine therapy	Infant died 10 minutes after birth; had hydrocephalus, bilateral cleft lip and palate
1983	Newman[68]	Case1: Sulfasalazine, Prednisolone Case2: Sulfasalazine	Case report	Throughout pregnancy	Three infants born to two mothers with inflammatory bowel disease receiving daily sulfasalazine therapy	Case 1: Stillborn twins with urinary tract abnormalities. Case 2: Infant died at 10 days of age and had coarctation of the aorta and a ventricular septal defect
1988	Hoo[69]	Sulfasalazine	Case report	Throughout pregnancy	Mother received daily sulfasalazine therapy for ulcerative colitis	Infant had coarctation of the aorta and a ventricular septal defect
2000	Richardson[70]	Case 1: TMP-SMZ, zidovudine, zalcitabine Case 2: TMP-SMZ, stavudine, didanosine, nevirapine, vitamin B	Case report	Throughout pregnancy	Two mothers receiving antiretrovirals and TMP-SMZ for HIV infection	Case 1: Infant born with lumbar spine hemivertebra Case 2: Elective termination of pregnancy, autopsy revealed ventriculomegally, Arnold-Chiari malformation, spina bifida, and meningomyelocoele
2000	Hernandez-Diaz[61]	Dihydrofolate reductase inhibitors: Trimethoprim, Triamterene and Sulfasalazine	Case-control study	Months 2 and 3	6932 infants with congenital abnormalities and 8387 controls	Higher proportion of mothers of infants with oral clefts (RR 2.6, 95% CI 1.1-6.1) and cardiovascular defects (RR 3.4, 95% CI 1.8-6.4) took dihydrofolate reductase inhibitors – 17/8387 (0.2%) control-mothers; 23/3870 (0.6%) cardiovascular defects case-mothers; 9/1962 (0.5%) oral clefts case-mothers
2001	Hernandez-Diaz[62]	Trimethoprim	Case-control study	Trimester 1	1242 infants with neural-tube defects and 6660 controls	Higher proportion of mothers of infants with neural tube defects took trimethoprim (OR 4.8, 95% CI 1.5-16.1) – 5/1242 (0.4%) case-mothers versus 8/6660 (0.1%) control-mothers
2001	Czeizel[63]	Trimethoprim-Sulfonamides	Case-control study	Month 2 and 3	22,865 pregnant women who had newborns or fetuses with congenital abnormalities and 38,151 controls	Higher proportion of mothers of infants with cardiovascular and urinary tract malformations took trimethoprim-sulfonamides – TMP-SMZ (OR 1.3, 95% CI 1.1-1.5): 351/22865 (1.5%) case-mothers versus 443/38151 (1.2%) control-mothers; trimethoprim-sulfamethazine (OR 1.9, 95% CI 1.3-3.0): 45/22865 (0.2%) case-mothers versus 39/38151 (0.1%) control-mothers

Table 3: Congenital abnormalities – Evidence for increased risk *(continued)*

Year	Author	Drug	Report type	Exposure period	Participants	Main findings
2001	Jungmann[65]	Folate antagonists (including TMP-SMZ, pyrimethamine, and carbamazepine) and different antiretrovirals	Cohort study	Trimester 1	195 HIV-infected mothers	Infants exposed to both antiretrovirals and folate antagonists in 1st trimester had an increased risk of congenital abnormalities when compared to infants not exposed (OR 7.10, 95% CI 1.5, 34.2): 3/13 (23.1%) with abnormalities among infants exposed, 6/148 (4%) among infants not exposed
2002	Rojansky[71]	TMP-SMZ	Case report	Week 7-9	Mother treated daily for upper respiratory disease. She was also treated with erythromycin for 2 weeks, and used topical minoxidil before and throughout pregnancy	Infant had caudal regression syndrome
2004	Czeizel[64]	Sulfonamides	Case-control study	Month 2 and 3	22,843 infants with congenital abnormalities and 38,151 controls	Higher proportion of mothers of infants with cardiovascular malformation (POR 3.5, 95% CI 1.9-6.4) and club foot (POR 2.6, 95% CI 1.1-6.2) took sulfonamides –38/38151 (0.1%) control-mothers; 14/4479 (0.3%) cardiovascular malformation case-mothers; 6/2424 (0.2%) club foot case-mothers

RR: relative risk; OR: odds ratio; CI: Confidence interval; POR: Prevalence odds ratio.

cy[66]. From 1980 to 1988, three case reports described five cases of multiple congenital abnormalities in the offspring of women who received daily sulfasalazine therapy for inflammatory bowel disease throughout their pregnancies[67-69]. Reported abnormalities included an infant with cleft lip, cleft palate, and hydrocephalus[67]; stillborn twins, both with urinary tract abnormalities and one with coarctation of the aorta and a ventricular septal defect[68]; and an infant with coarctation of the aorta, a ventricular septal defect, and macrocephaly[69]. In 2000 a report described two cases of HIV-positive women treated with daily TMP-SMZ and antiretrovirals who had offspring with abnormalities that included lumbar hemivertebra, ventriculomegally, and spina bifida[70]. Finally, a 2002 report described caudal regression syndrome in a fetus whose mother had been treated in the first trimester with TMP-SMZ and erythromycin, and who had also been treated with topical minoxidil before and throughout pregnancy[71].

Congenital abnormalities - Evidence for safety

A 1969 report comparing infants of 120 women treated for bacteriuria with TMP-SMZ and 66 women treated with placebo during all trimesters of pregnancy found four cases of congenital abnormalities in the TMP-SMZ group and three cases in the placebo group[72,73] (Table 4). A 1969 case-control study of 833 mothers of infants with congenital abnormalities in Wales found no association between maternal ingestion of sulfonamides throughout pregnancy and any type of congenital abnormalities[74]. A 1971 case report described a pregnant woman with actinomycosis treated daily with TMP-SMZ through eight months gestation, who gave birth to a normal, healthy infant[75].

A 1983 study of 44 women comparing single-dose to five-day treatment with TMP-SMZ for bacteriuria during the first trimester of pregnancy described no congenital abnormalities in their infants, but reported one stillbirth in a woman treated for five days[76,77]. In 1990 evaluation of data from 6228 mothers of infants with abnormalities in the Hungarian Case-Control Surveillance of Congenital Anomalies Study found no evidence of teratogenicity associated with maternal TMP-SMZ use[78]. An evaluation of the 22,865 infants or fetuses with congenital abnormalities from the same database in 2001 also found no evidence of increased prevalence of congenital abnormalities associated with maternal sulfasalazine use[79]. In 1996 a study of 110 infants with gastroschisis from the California Birth

Table 4: Congenital Abnormalities – Evidence for safety

Year	Author	Drug	Report type	Exposure period	Participants	Main findings
1969	Williams[72,73]*	TMP-SMZ	Clinical trial	All trimesters	120 women treated with TMP-SMZ and 66 women treated with placebo	Four cases of congenital abnormalities in TMP-SMZ group compared with three cases in placebo group. No statistical measure of association noted
1969	Richards[74]	Sulfonamides	Case-control study	All trimesters	833 mothers of infants with congenital abnormalities and 833 controls	No association between maternal ingestion of sulfonamides and any type of congenital abnormalities – First trimester: 4/833 (0.5%) case-mothers took sulfonamides versus 6/833 (0.7%) control-mothers; second and third trimesters: 15/833 (1.8%) case-mothers versus 8/833 (1.0%) control-mothers. No statistical measure of association noted
1971	Ochoa[75]	TMP-SMZ	Case report	Month 1-8	Woman treated daily for actinomycosis before and during pregnancy	Normal infant delivered without congenital abnormalities
1983	Bailey[76,77]*	TMP-SMZ	Randomized clinical trial	First trimester	44 women randomly assigned to treatment with either single dose or a 5-day course of TMP-SMZ for bacteriuria	One stillbirth in group treated with 5-day course, no congenital abnormalities reported. No statistical measure of association noted
1990	Czeizel[78]	TMP-SMZ	Case-control study	All trimesters	6228 mothers of infants with congenital abnormalities and 9893 controls	Higher proportion of mothers of infants with congenital abnormalities ingested TMP-SMZ ($p < 0.01$), but authors concluded that the analysis "did not indicate any teratogenicity of co-trimoxazole" because a higher frequency of maternal disorders in the case mothers probably explained the higher TMP-SMZ use, and use was not higher during the critical periods for teratogenicity in specific congenital abnormality groups – 144/6228 (2.31%) case-mothers ingested TMP-SMZ versus 124/9893 (1.25%) control-mothers
1996	Torfs[79]	Sulfonamides	Case-control study	First trimester	110 infants with gastroschisis and 220 controls	No association between maternal ingestion of sulfonamides and gastroschisis found (OR 0.39, 95% CI 0.05-3.42) – 1/110 (0.9%) case-mothers took sulfonamides versus 5/220 (2.3%) control-mothers
2001	Norgard[80]	Sulfasalazine	Case-control study	All trimesters	Mothers of 22,865 infants or fetuses with congenital abnormalities and 38,151 controls	No association between maternal ingestion of sulfasalazine and congenital abnormalities found (OR 1.2, 95% CI 0.6-2.1) – 17/22865 (0.07%) case-mothers took sulfasalazine versus 26/38151 (0.07%) control-mothers
2003	Ratanajmit[54]	Sulfamethizole	Cohort Study	30 days before conception to end of first trimester	2173 mothers who received prescription in first trimester or 30 days before, compared to 60,175 mothers who did not	No association between receipt of prescription for sulfamethizole and congenital abnormalities found (OR 1.17, 95% CI 0.95-1.43) – 101/2173 (4.6%) mothers of infants with malformations received prescription versus 2379/60175 (4.0%) who did not

Defects Monitoring Program found no association between maternal ingestion of sulfonamides and gastroschisis[80]. In 2003 a cohort study in Denmark found no association between maternal sulfamethizole ingestion and congenital abnormality[54]. Finally, reports have provided evidence of the safety of sulfadoxine-pyrimethamine use during the second and third trimesters of pregnancy for intermittent preventive treatment of malaria[81-85].

Table 5 – Guidelines providing recommendations for use of trimethoprim-sulfamethoxazole as prophylaxis against opportunistic infections for HIV-infected women during pregnancy

Source	Trimester	Use During Breastfeeding	CD4 Count Criteria	Clinical Criteria	Drug regimen	Comment on risk/benefit of TMP-SMZ
WHO/UNAIDS[15]	Pregnant women after the first trimester	Does not address	All asymptomatic HIV-positive adults (age > 13years) with CD4+ cell count ≤ 500/µl	All adults with symptomatic HIV disease (WHO stage 2, 3 or 4)	One double-strength or 2 single-strength tablets daily	None
USPHS/IDSA[22]	Prophylaxis should be administered as for other adults and adolescents but providers may choose to withhold prophylaxis during the first trimester	Does not address	(i) All adults and adolescents with CD4+ cell count < 200/µl (ii) Other considerations for prophylaxis: (a) persons with CD4+ cell count < 14%; (b) persons with CD4+ cell count < 250/µl in settings where impossible to monitor CD4+ cell counts every 3 months	(i) History of oropharyngeal candidiasis (ii) History of PCP (iii) Other considerations for prophylaxis: persons with history of an AIDS-defining illness (ii) Alternate regimens:	(i) One double-strength tablet daily (a) One double-strength tablets three times per week; (b) One single-strength tablet daily	"... because of theoretical concerns regarding possible teratogenicity associated with drug exposures during the first trimester, providers may choose to withhold prophylaxis during the first trimester"
Canadian Consensus Guidelines[86]	Not specified	Does not address	Immunocompromised women with CD4+ cell count ≤ 200/µl	"Immunocompromised"	"According to usual adult guidelines"	"TMP-SMZ is relatively safe for use in pregnancy and is the first choice for PCP prophylaxis. The increased risk of neonatal hyperbilirubinemia related to use of this drug in the third trimester is acceptable and is outweighed by the serious impact of PCP on the mother and infant."
Columbia Clinical Manual[16]	Throughout pregnancy, including close to the time of delivery, and during the postpartum period while breastfeeding.	Yes	CD4+ cell count ≤ 200/µl	WHO stage 3 or 4 disease; previously diagnosed PCP	One double-strength tablet daily or three times weekly	"There is a very small risk of infant kernicterus (hyperbilirubinemia) associated with maternal use of sulfa drugs such as cotrimoxazole, but the risks of PCP and severe infections in women with advanced HIV/AIDS significantly outweigh this concern."
South African Department of Health Policy Guidelines[87]	Not specified	Does not address	CD4+ cell count < 200/µl	Presence of clinical signs of advanced immune deficiency	Two single-strength tablets daily	None
Uganda National Policy Guidelines[17]	All pregnant women after the first trimester	Does not address	No specific CD4+ cell count criteria stated	No specific clinical criteria stated	One double-strength or 2 single-strength tablets daily	None

TMP-SMZ: Trimethoprim/sulfamethoxazole; PCP – Pneumocystis jiroveci pneumonia
* Same study reported in 2 articles

Existing guidelines

Existing guidelines recommend that HIV-infected pregnant women receive TMP-SMZ prophylaxis (Table 5). They differ, however, with regards to stage of disease at initiation of prophylaxis, need for CD4+ T-lymphocyte testing, and administration during the first trimester. For persons living with HIV/AIDS in Africa, pro-

visional recommendations from the World Health Organization (WHO) are that TMP-SMZ prophylaxis be offered as primary prophylaxis to all HIV-positive adults with symptomatic HIV disease (WHO stage 2, 3, or 4), asymptomatic individuals who have a CD4+ T-lymphocyte count ≤ 500, and pregnant women after the first trimester[15].

The United States Public Health Service (USPHS) and Infectious Diseases Society of America (IDSA) recommend that HIV-infected pregnant women with a CD4+ T-lymphocyte count of < 200/µl or a history of oropharyngeal candidiasis receive PCP prophylaxis. However, USPHS/IDSA guidelines for pregnant women note that providers may choose to withhold prophylaxis during the first trimester, in which case aerosolized pentamidine may be considered[22]. USPHS/IDSA further recommends that children born to HIV-infected mothers begin primary prophylaxis with TMP-SMZ at about 4-6 weeks of age. Canadian consensus guidelines for the management of HIV-positive pregnant women recommend PCP prophylaxis for women with CD4+ T-lymphocyte count ≤ 200/µl[86].

For resource-limited communities, the Columbia Clinical Manual recommends giving TMP-SMZ to all pregnant women with i) WHO stage 3 or 4 disease, irrespective of CD4+ T-lymphocyte count; ii) a CD4+ T-lymphocyte count ≤ 200/µl irrespective of WHO stage; or iii) all patients with previously diagnosed PCP[16]. The South African Department of Health policy guidelines recommend PCP prophylaxis with TMP-SMZ for pregnant women with CD4+ T-lymphocyte counts < 200/µl or with clinical signs of advanced immune deficiency[87]. Uganda's national policy guidelines recommend prophylaxis be given to all HIV-positive pregnant women after the first trimester, regardless of CD4+ T-lymphocyte count, noting that HIV-positive pregnant women should not be given concurrent sulfadoxine-pyrimethamine therapy for malaria since TMP-SMZ is effective for malaria prophylaxis[17].

Discussion

Reports documenting the association of hyperbilirubinemia and kernicterus with sulfonamide use during pregnancy are derived mostly from small studies and retrospective case series that examined sulfonamides other than sulfamethoxazole, or that did not differentiate the effects of sulfonamides from other causes of hyperbilirubinemia[33-38]. The often-cited study by Silverman that found increased risk of mortality and kernicterus associated with sulfisoxazole involved postnatal, not *in utero,* exposure to the drug among premature infants who are highly susceptible to hyperbilirubinemia[35]. Multiple other studies have shown that the use of sulfonamides is not associated with hyperbilirubinemia when taken by mothers during pregnancy and when breastfeeding[39-53]. We found no reports of neonatal kernicterus attributable to maternal ingestion of sulfonamides.

There is mixed evidence linking ingestion of TMP-SMZ and other sulfonamides in early pregnancy to elevated risks of oral clefts, neural tube defects, and cardiovascular and urinary tract abnormalities. Limited data suggest that supplementation with folic acid may ameliorate this risk. The available information is complicated by inability of some large studies to differentiate between women who took TMP-SMZ or other sulfonamides early in pregnancy during organogenesis and those who took the drugs later in pregnancy after completion of organogenesis. Additionally, smaller studies may have insufficient sample sizes to detect rare events. As several large-scale studies have found differing results, the potential teratogenicity of TMP-SMZ is still uncertain, but the drug likely poses at least a minimal risk.

It is unlikely that a definitive trial will be performed in sub-Saharan Africa evaluating the safety of daily TMP-SMZ prophylaxis during pregnancy or during breastfeeding. It would be operationally challenging in resource-limited settings to establish capacity to perform serial bilirubin determinations, to provide phototherapy and exchange transfusions when needed, to train and outfit pathologists to diagnose kernicterus postmortem, and to maintain registries to detect rare outcomes such as congenital abnormalities potentially related to first trimester *in utero* exposure to a teratogen. We must rely therefore on the existing evidence to make decisions about TMP-SMZ use for prophylaxis in HIV-infected pregnant women.

Some guidelines recommend TMP-SMZ use for prophylaxis in HIV-infected pregnant women only after the first trimester because of continued concern about its potential teratogenicity[15,17]. Others, however, do not address first trimester use[86,87], leave it up to the clinical judgment of the provider[22], or recommend use throughout pregnancy including the first trimester[16]. The decision to use TMP-SMZ in the first trimester for prophylaxis should weigh the potential risk for teratogenicity against the potential morbidity associated with PCP and other infections in pregnancy. Given the mixed evidence linking ingestion of TMP-SMZ to congenital abnormalities, use in the first trimester should target

women at highest risk for HIV-related illness (such as those with CD4+ cell counts < 200, those with clinical evidence of advanced disease, or those who have been previously diagnosed with PCP). The benefit of improved morbidity and mortality with TMP-SMZ prophylaxis among these high-risk women may outweigh the small risk to the fetus. Women who become pregnant while taking TMP-SMZ at prophylactic dosages should be counseled that the potential risk of teratogenicity is small. Given that trimethoprim and sulfamethoxazole are known antagonists of folic acid, the usual recommendation of periconceptional folic acid supplementation should be especially emphasized for women on TMP-SMZ prophylaxis.

Few guidelines recommending TMP-SMZ use for prophylaxis in HIV-infected pregnant women specifically address use during the third trimester and during breastfeeding[16]. Multiple studies have shown that the risk of hyperbilirubinemia and kernicterus secondary to TMP-SMZ prophylaxis is very low, and that the benefits of use greatly outweigh the risks in HIV-infected pregnant women. For HIV-infected women in developing countries who may elect to breastfeed when no safe, affordable alternatives are available, daily TMP-SMZ prophylaxis should be at least as safe as *in utero* exposure and likely safer, since both trimethoprim and sulfamethoxazole are excreted only in low concentrations in breast milk. Guidelines should therefore dispel ambiguity by clearly encouraging continued prophylactic use of TMP-SMZ by HIV-infected women in the third trimester and during breastfeeding.

Conclusion

TMP-SMZ prophylaxis can provide substantial benefits for HIV-infected pregnant women; recent data from Zambia indicate significantly improved birth outcomes among HIV-infected pregnant women with CD4+ cell counts < 200 who receive routine TMP-SMZ prophylaxis[88]. Pregnancy poses a special challenge for HIV-infected women, as clinicians must weigh the benefits of drugs used to treat HIV disease against the potential harm their use poses to the fetus. Prophylaxis against PCP and other opportunistic infections is an important component of HIV/AIDS care that should be made available to all eligible HIV-infected individuals, including pregnant women. For HIV-infected pregnant women, the substantial benefits of TMP-SMZ prophylaxis should be considered in conjunction with the operational limitations of interrupting prophylaxis around term. Given the comparatively substantial benefits of TMP-SMZ prophylaxis for HIV-infected women living in resource-limited settings, this review indicates that it is safe to abide by the WHO guidelines recommending daily TMP-SMZ prophylaxis for HIV-infected pregnant women.

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Disclaimer

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