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Safety of cotrimoxazole in pregnancy: a systematic review and meta-analysis

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Abstract

Introduction—Cotrimoxazole is widely prescribed to treat a range of infections and for HIV-infected individuals it is administered as prophylaxis to protect against opportunistic infections. Some reports suggest that fetuses exposed to cotrimoxazole during early pregnancy may have an increased risk of congenital anomalies. We carried out this systematic review in order to update the evidence of cotrimoxazole safety in pregnancy.

Methods—Three databases and one conference abstract site were searched in duplicate up to 31 October, 2013 for studies reporting adverse maternal and infant outcomes among women receiving cotrimoxazole during pregnancy. This search was updated in MEDLINE via PUBMED to 28 April 2014. Studies were included irrespective of HIV-infection status or the presence of other co-infections. Our primary outcome was birth defects of any kind. Secondary outcomes included spontaneous abortions, terminations of pregnancy, stillbirths, preterm deliveries, and drug-associated toxicity.

Results—24 studies were included for review. There were 232 infants with congenital anomalies among 4196 women receiving cotrimoxazole during pregnancy, giving an overall pooled prevalence of 3.5% (95% CI 1.8–5.1%; τ^2 0.03). Three studies reported 31 infants with neural tube defects, giving a crude prevalence of 0.7% (95%CI 0.5–1.0%) with most data (29 neural tube defects) coming from a single study. The majority of adverse drug reactions were mild. The quality of the evidence was very low.

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There are no conflicts of interest.

Conclusions—The findings of this review support continued recommendations for cotrimoxazole as a priority intervention for HIV-infected pregnant women. It is critical to improve data collection on maternal and infant outcomes.

Keywords

birth defects; congenital anomalies; cotrimoxazole; HIV/AIDS; pregnancy

Introduction

Cotrimoxazole (trimethoprim–sulfamethoxazole) is a safe, effective, low-cost combination antibiotic that is widely prescribed to treat a range of bacterial, parasitic, and fungal infections. For HIV-infected individuals, cotrimoxazole administered as prophylaxis provides protection against the opportunistic infection pathogens *Pneumocystis jirovecii* and *Toxoplasma gondii.* It has also been shown to be protective against malaria, bacterial pneumonia and diarrheal disease in resource-limited countries, resulting in a reduced risk of death in clinical trials in these settings.[1,2] For HIV-infected pregnant women, the use of prophylactic cotrimoxazole is associated with a reduction in preterm delivery and neonatal mortality in their HIV-exposed infants.[3] Since 2006, the World Health Organization (WHO) has recommended that cotrimoxazole prophylaxis should be provided to all HIV-infected individuals with a CD4 cell count <350 per mm^3, particularly in resource-limited settings where bacterial infections and malaria are prevalent.[4]

Cotrimoxazole provides sequential and synergistic inhibition of bacterial folate metabolism through its action on dihydropteroate synthesase and dihydrofolate reductase (DHFR) enzymes, inhibiting the biosynthesis of nucleic acids. Although more selective for the bacterial than the human DHFR isoenzyme, the drug can nevertheless interfere with human folate metabolism.[5] Pregnancy is associated with rapid cell division in the unborn child, and folate is essential for fetal development because of its critical role in DNA synthesis.[6] Folate deficiency in early pregnancy is associated with adverse pregnancy outcomes, including an increased risk of neural tube defects and other congenital defects.[7] Both drugs, trimethoprim and sulfamethoxazole, cross the placental barrier, reaching peak fetal levels within 3 hours of administration; fetal levels of sulfamethoxazole average 70–90% of maternal levels while those of trimethoprim are comparable to maternal levels.[8,9] Pregnancy exposure studies carried out in rats and rabbits[10] and small, retrospective studies in humans have reported some evidence of congenital anomalies with first trimester cotrimoxazole exposure.[11] Cotrimoxazole is listed as a Class D drug by the Food and Drug Administration[12,13] meaning that there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or from studies in humans, but the potential benefits of the drug may warrant its use in pregnancy despite the potential risks.

In the United States, guidelines for the management of HIV-infected adults and adolescents acknowledge a possible association between first-trimester exposure to trimethoprim and an increased risk of congenital anomalies; cotrimoxazole use in the first-trimester of pregnancy is still recommended for the treatment of *Pneumocystis* pneumonia because of its considerable benefit, while for prophylaxis the guidelines state that health care providers

may consider using alternative regimens.[14] WHO's 2006 guidelines recommend that women who fulfill the criteria for cotrimoxazole prophylaxis should continue cotrimoxazole throughout their pregnancy, since the risk of life-threatening infections outweighs the potential risk of congenital abnormalities.[4]

We carried out this systematic review in order to update the evidence of cotrimoxazole safety in pregnancy to inform a revision of WHO's guidelines for cotrimoxazole prophylaxis in pregnant women infected with HIV.

Methods

Search strategy and study selection

Using a pre-defined protocol incorporating a compound search strategy (Supplementary Appendix 1), we searched EMBASE, MEDLINE via PubMed and *The Cochrane Library* up to 31 October, 2013 for studies reporting adverse maternal and infant outcomes among women exposed to cotrimoxazole during pregnancy. The search was updated in MEDLINE via PubMed up to 28 April 2014. We also reviewed online abstracts of all conferences of the International AIDS Society using single terms for cotrimoxazole (up to Kuala Lumpur, June 2013) and hand searched bibliographies of previously published systematic and non-systematic reviews and other relevant articles. No language or geographical restrictions were applied.

Two reviewers (N.F, Z.S.), working independently, scanned all titles for eligibility according to predefined inclusion criteria. Once all potentially relevant full-text articles and abstracts were identified, we consulted clinical experts (L.M., E.A, J. J.) to achieve consensus regarding eligibility criteria. Studies were included irrespective of HIV-infection status or the presence of other co-infections. Where infections were associated with outcomes under assessment (e.g. brucellosis and stillbirth), however, we did not pool data due to confounding by indication. We made no distinction regarding whether cotrimoxazole was provided for prophylaxis or treatment. Studies assessing sulfonamide drugs alone were excluded.

Data extraction

Data extraction was conducted independently and in duplicate using a pre-piloted data extraction form (Z.S., N.F.) and subsequently verified by two other reviewers (J.J., L.M.). Information was extracted on study size, setting, and population; co-infection status; period and duration of exposure; and birth outcomes. Our primary outcome was birth defects of any kind. Secondary outcomes included spontaneous abortions, terminations of pregnancy, stillbirths, preterm deliveries, and drug-associated toxicity.

Assessment of methodological quality

Risk of bias was assessed according to six criteria: direct ascertainment of cotrimoxazole use, adjustment for confounders, prospective study design, outcomes reported by trimester, outcomes reported by folate supplement use, and potential for confounding by indication.

This risk of bias assessment was used to inform the overall assessment of the quality of the evidence, which followed the GRADE approach.[15]

Data analysis

Point estimates and 95% confidence intervals (95% CI) were calculated for the proportion of congenital anomalies reported among live births for each study. Where possible, we excluded spontaneous and induced abortions and stillbirths from the numerator and denominator for the estimate of congenital anomalies, consistent with current reporting conventions. Because of heterogeneity between studies, the overall prevalence of congenital anomalies was estimated by pooling data from each study using a DerSimonian-Laird random effects model[16] following arcsine square-root transformation to stabilize the variance of the raw proportions,[17] and subsequent back transformation to the original scale.[18] Data derived from randomized trials were pooled together with data from observational studies using random effects analysis, consistent with recommended approaches for systematic reviews of adverse events.[19] The following pre-planned subgroup analyses were conducted for the pooled prevalence estimate of congenital anomalies: trimester of cotrimoxazole exposure (first trimester versus second or third trimester), study design, and provision of folate supplementation (≥ 50% versus < 50% of the cohort). For outlier studies, we undertook a leave-one-out meta-analysis in which each study was dropped in turn to assess its influence on the overall pooled prevalence.[20] Odds ratios (OR) and corresponding 95% CIs were calculated for data derived from case-control studies, and where appropriate, the data were pooled, also using random effects models. Data for secondary outcomes were not pooled because background prevalence rates are known to vary considerably between study settings. Heterogeneity was assessed using both the I^2 and τ^2 statistics.[21] All analyses were conducted using STATA (version 12, www.stata.com) and GRADE Pro (www.gradeworkinggroup.org).

Results

Characteristics of included studies

From a total of 2344 publications initially screened, 24 met the inclusion criteria and were taken through for full review (Figure 1).[3,22–41] One paper reported the results of several studies in a single paper,[26] one study reported data in two separate publications,[3042] and data from another, unpublished study, was reported in a review article.[36] Two studies reported data from the Danish national pregnancy registry during overlapping time periods: one reported the risk of miscarriage among all births,[22] the other reported the risk of congenital anomalies among live births.[23] Four studies were carried out in sub-Saharan Africa (Benin,[43] Malawi,[44] Togo,[45] and Zambia[3]), while the rest were carried out in high-income settings. Five studies reported outcomes among HIV-infected women.[3,32,43–45] There were 4 surveillance studies, 6 randomized controlled trials (RCT), 5 case-control studies, and 9 cohort studies. The reporting period ranged from 1973[26] to 2012[45], with over half of the studies reporting data collected from 2002 onwards. Study characteristics are summarized in Table 1.

Congenital anomalies

Prevalence of congenital anomalies—Sixteen studies reported 232 infants with congenital anomalies among 4196 women receiving cotrimoxazole during pregnancy,[3,23–28,32–34,36,37,39,41,43,45] summarized in Table 2. The remaining eight studies were not included in this analysis for the following reasons: five were case-control studies,[29–31,38,46] while the remaining three studies reported only data regarding secondary outcomes.[22,4440] The prevalence of congenital anomalies ranged from 0.3% (95% CI 0.3–2.8%) to 16.3% (95% CI 0.8–45.7%), with an overall pooled prevalence of 3.5% (95% CI 1.8–5.1%; I^2 84.9%, τ^2 0.03).[34] The pooled prevalence was higher for studies that included pregnant women receiving cotrimoxazole during the first trimester of pregnancy (4.8%, 95%CI 0.6–8.9%) compared to studies in which there were no first trimester exposures (1.4%, 95%CI 0.3–2.4%). These differences were, however, not found to be statistically significant (P=0.1). These data are summarized in Figure 2. When comparing the reported prevalence of congenital anomalies by study design, the pooled prevalence was higher for population surveillance studies (7.8%, 95%CI 3.6–11.9%) compared to RCTs (1.4%, 95%CI 0.5–2.4%), prospective cohort studies (2.1%, 95%CI 0–5.6%) or retrospective cohorts (2.0%, 95%CI 0.1–3.6%). The pooled prevalence of birth defects in infants in studies that included HIV-infected pregnant women[3,32,43,45] (1.7%, 95%CI 0.6–2.7%) was lower compared to the overall prevalence in all women.

We conducted a sensitivity analysis in which the pooled prevalence was assessed after dropping each study in turn in order to determine the degree of influence of any single study on the overall pooled prevalence estimate of congenital anomalies. In this analysis, the pooled prevalence was reduced from 3.5% (1.8–5.1%) to 2.6% (95% 1.2–4.0) when one study[34] was dropped from the analysis (Supplementary Table 1). This study differed from the other studies in two notable ways: first, fetal anomalies were diagnosed in utero; second, around half of the cohort were Bedouins in Israel, a community in which there is increased consanguinity.[47] Incidence of birth defects were reported to be higher among the Bedouin community during the reporting period of this study.[48] These factors may have led to both a higher ascertainment of congenital anomalies, and a higher background prevalence of anomalies in this cohort.

Among the 16 studies reporting on the prevalence of congenital anomalies, three studies reported 31 infants with neural tube defects, giving a crude prevalence of 0.7% (95%CI 0.5–1.0%). These data were also dominated by the study described above,[34] which contributed 29 of 31 neural tube defects.

Odds of congenital anomalies—Four case-control studies, reported in five articles,[29–31,42,46] provided data on the OR of congenital anomalies comparing cotrimoxazole exposure among cases and controls. There was no statistically significant difference in the risk of overall congenital anomalies (2 studies; OR 0.6, 95%CI 0.1–3.4), with high heterogeneity between studies (I^2 84%, τ^2 1.2). An increased risk was reported for neural tube defects (1 study; OR 3.4, 95%CI 1.1–10.3;), cardiovascular defects (1 study; OR 2.9, 95%CI 1.6–5.5), and oral clefts (2 studies; OR 2.0, 95% CI 1.2–3.4; I^2 0%, τ^2 0) but not urinary tract defects (1 study; OR 0.9, 95% CI 0.2–3.9).

Secondary outcomes

Five studies provided data on maternal toxicity.[26,27,39,43,45] Of 714 women exposed to cotrimoxazole during pregnancy in these studies (490 with HIV infection), 31 (4.3%) experienced an adverse drug reaction; the majority of events were mild with only 4 events (0.6%) resulting in treatment discontinuation. One study provided data on neonatal jaundice, reporting one case out of 67 exposures.[3] Other reported birth outcomes included stillbirths (6 studies), spontaneous abortions (6 studies), small for gestational age (7 studies), and pre-term birth (6 studies). Data were not pooled due to the limited data reported for these outcomes, differing background population rates, and risk of confounding by indication. No cases of kernicterus were reported. These outcomes are summarized in Supplementary Tables 2 and 3.

Assessment of methodological quality

Risk of bias was considered to be moderate to high. Seven studies did not directly ascertain cotrimoxazole use, 15 studies did not assess the potential influence of confounders, 14 studies used retrospective designs, 9 studies did not disaggregate outcomes by trimester of exposure, 17 studies did not report on folate use, and 7 studies were at risk of confounding by indication for secondary outcomes (Supplementary Table 4). The risk of publication bias was considered to be high, considering that cohorts among whom adverse outcomes occurred are more likely to be documented and published. This was not formally assessed due to the small number of identified studies. Overall, the GRADE assessment determined that the quality of the evidence contributing to the assessment of prevalence and odds of congenital anomalies was very low. This information is summarized in Supplementary Tables 5 and 6.

Conclusions

Cotrimoxazole has been commonly prescribed for over forty years for the treatment of a wide range of infections, and has been recommended as life-saving prophylaxis by the WHO for all HIV-infected individuals with low CD4 cell count, including pregnant women. Despite its long history of widespread use, this review found very limited evaluable data on maternal and infant outcomes associated with cotrimoxazole exposure during pregnancy. While some studies included in this review suggested that cotrimoxazole exposure in pregnancy was associated with congenital abnormalities, the overall pooled prevalence was not significantly higher than the reported rates in the general population.[49] In the United States, the prevalence of congenital anomalies is 2.7%[50] while in sub-Saharan Africa, the reported prevalence ranges from 0.4% to 3.7%.[51] Evidence from case-control studies suggests a potential increased risk of certain specific congenital anomalies, including neural tube defects. The crude prevalence of neural tube defects was 0.7%, which is higher than that reported among the general population in the United States (0.04–0.06% before regular folic acid fortification),[52] United Kingdom (0.14%)[53] and South Africa (0.36%);[54] however, most of the defects were reported by one study in which prenatal ultrasound screening was standard and that included a population with increased consanguinity[34]. Thus, the poor quality of the data prevents any definitive conclusions from being drawn. Nevertheless, this review found some reassuring evidence of cotrimoxazole safety. Although the data were

limited, maternal treatment limiting adverse events were rare. There was no evidence of excessive rates of infant jaundice associated with cotrimoxazole exposure in pregnancy, although only 1 study reported on neonatal jaundice.

A previous systematic assessment of cotrimoxazole safety in pregnancy, carried out in 2006, took a broad approach that considered any sulfonamide exposure, concluding that there was mixed evidence about safety in pregnancy; overall estimates of risk were not calculated.[9] We limited our review to cotrimoxazole, but did include HIV-uninfected cohorts as well as exposure to cotrimoxazole for both treatment and for prophylaxis of various infectious diseases. Our search strategy and inclusion criteria allowed for the identification of over 4,000 exposures in randomized trials and observational cohort studies that could contribute to estimating prevalence of congenital anomalies, with additional information provided by case-control studies. Confidence intervals were calculated for outcomes of individual studies and for pooled estimates in order to reflect the level of uncertainty around the prevalence estimates. In order to compensate for the limited number of studies reporting outcomes specifically for cotrimoxazole prophylaxis, we included studies in which pregnant women received cotrimoxazole for the treatment of various infections. The duration of drug exposure and the indication for its use – including for infections known to be associated with some of the secondary outcomes under assessment – differed considerably between these studies. Although the primary outcome of birth defects was not found to be influenced by infection status in sensitivity analyses, secondary outcomes should nevertheless be interpreted with particular caution given the risk of confounding by indication. Other methodological issues of concern included the retrospective nature of many studies, the inadequate reporting of timing and duration of cotrimoxazole exposure, the limited reporting of folate use and other potential confounders, and the likelihood of publication bias favoring the documentation and reporting of adverse outcomes. These limitations resulted in the quality of the evidence being rated as very low. Further studies are needed to improve judgment about the safety of cotrimoxazole in pregnancy.

Despite the widespread use of cotrimoxazole prophylaxis in HIV-infected individuals, including pregnant women, an important limitation of our review is the limited data found on birth outcomes in HIV-infected pregnant women receiving long-term cotrimoxazole prophylaxis. The majority of studies included in this review reported on short-term cotrimoxazole use for the treatment of various infectious diseases, such as urinary tract infections, brucellosis, toxoplasmosis or Q fever. Less than a quarter of data contributing to the prevalence assessment came from HIV-infected women, and only one of these studies (29 exposures) reported on first-trimester cotrimoxazole use; this study suggested that exposure to the combination of antiretroviral drugs and folate antagonists was associated with an increased risk of congenital abnormalities. In this study, of 32 women receiving folate antagonists in the first trimester, 3 were not exposed to cotrimoxazole but to other antifolates (pyrimethamine, carbamazepine) and only 13 women received both antiretroviral and anti-folate drugs (and the study did not delineate whether all 13 were exposed to cotrimoxazole or to the other anti-folates).[27] Almost all data on birth defects for HIV-infected women were from Africa, where concomitant nutritional deficiencies may be more common than in resource-rich countries.

This review highlights several areas for future research. First, improved surveillance is critical to gather data on cotrimoxazole exposure during pregnancy, as is the case for a number of drugs commonly used in the management of HIV/AIDS, notably efavirenz. This review found few reports from high HIV-burden, resource-limited settings, where cotrimoxazole prophylaxis is likely to be of most benefit. The lack of screening for congenital abnormalities and the high rate of unattended deliveries in these settings may change the programmatic implications of the results reported by this review. It will be critical for pregnancy outcome surveillance to include an evaluation of exposure to cotrimoxazole as well as antiretroviral drugs. Pregnancy outcome surveillance is being reinforced in several countries with the support of WHO and major donors, and the findings from this work will help inform future guidance. More data are needed for all important maternal and infant outcomes when using cotrimoxazole for prophylaxis in HIV-infected pregnant women, in particular in settings of high malaria prevalence, with outcomes disaggregated by trimester and duration of cotrimoxazole exposure, and where possible, reporting of relevant concomitant exposures (e.g., smoking, folate and other nutritional supplementation, use of other drugs). Finally, cotrimoxazole inhibits folic acid synthesis, and two studies included in this review suggested that periconceptional daily folic acid supplementation may reduce cotrimoxazole's potential teratogenic effect.[29,42] However, concomitant folate use may reduce the antibacterial effect of cotrimoxazole, which warrants further study.

In conclusion, the findings of this review support continued recommendations to provide cotrimoxazole prophylaxis to HIV-infected pregnant women. As with the use of any drug in pregnancy, the benefits of the drug need to be weighed against its potential risks. It is crucial that data collection on maternal and infant outcomes is improved to better assess the safety of cotrimoxazole use during pregnancy. Because of the substantial mortality reduction benefits associated with cotrimoxazole use in HIV-infected individuals with low immunity[1,2] and the particular vulnerability of HIV-infected pregnant women to diseases potentially preventable by cotrimoxazole such as malaria, continued recommendations for cotrimoxazole as a priority intervention for HIV-infected pregnant women is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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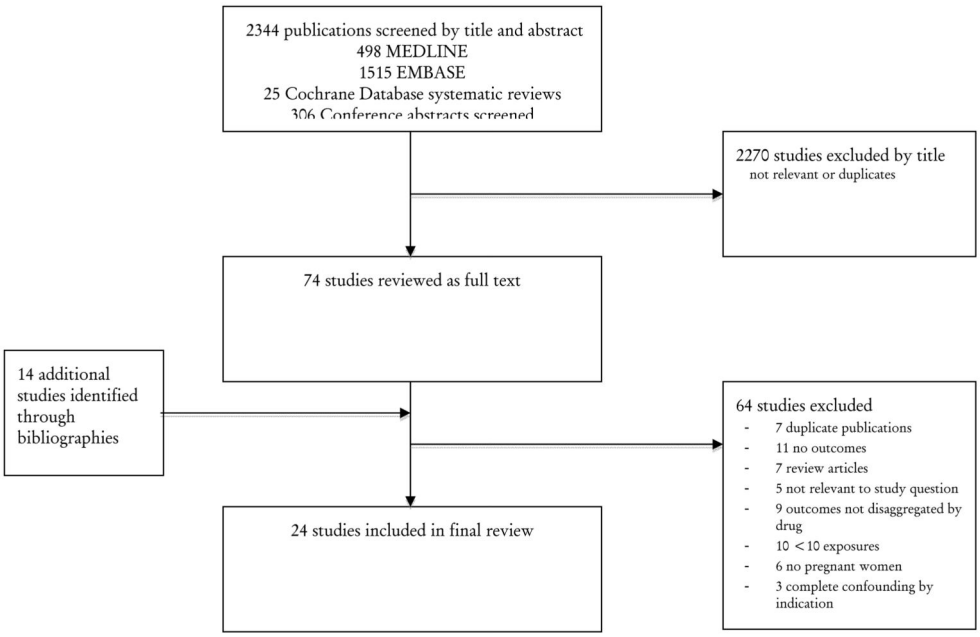

Figure 1.
Identification process for eligible studies

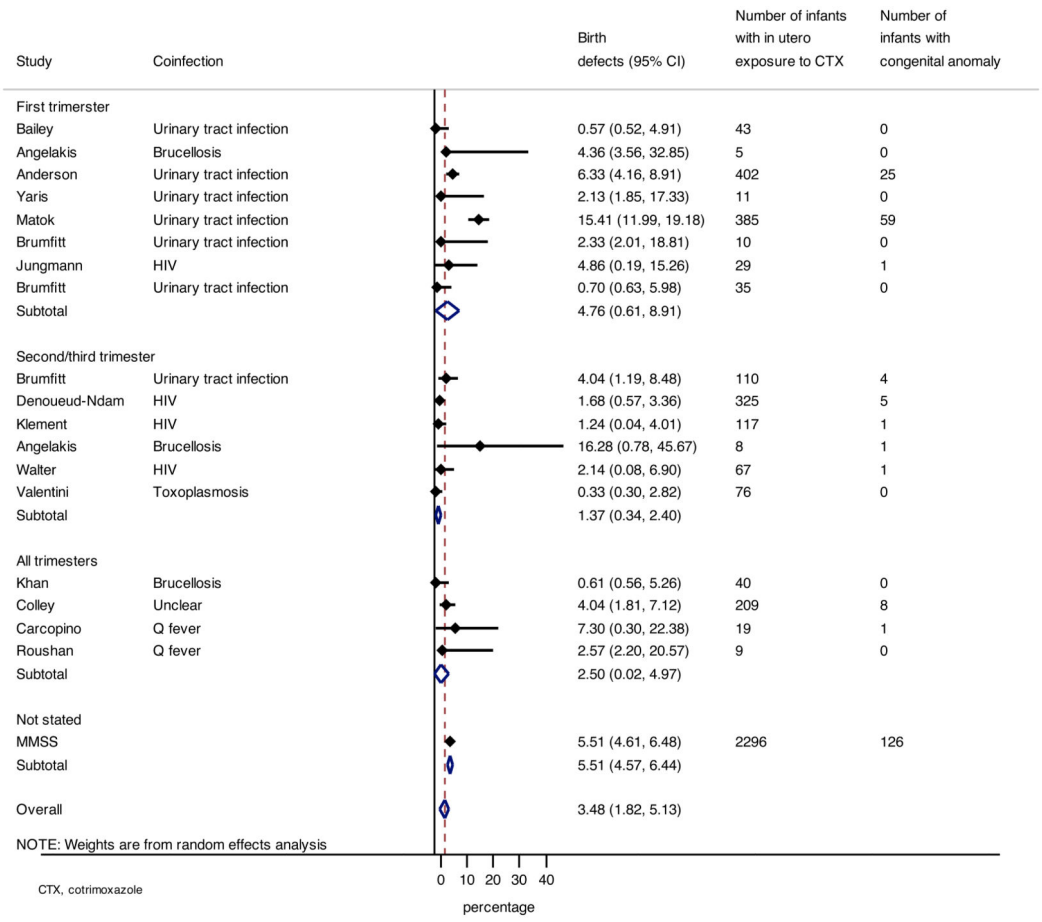

Figure 2.
Pooled prevalence of infant congenital anomalies by trimester

Table 1

Study Characteristics

Study	Design; setting	Reporting period	Overall study size	Numbers receiving CTX	Indication	HIV+	Dose	Timing	Duration	Main drug provided	Other drugs	Folate
Anderson *et al*, 2013[22]	Hospital registry cohort & Danish Fertility Registry; Denmark	1997–2007	931,504	265	UTI	0	NR	1st Trimester	NR	TMP or TMP+SMX	Sulfamethizole given to 34/265	NR
Anderson et al, 2013[23]	Danish Fertility Registry; Denmark	1997–2005	521,267	402	UTI (assumed)	0	NR	12 weeks prior to pregnancy	NR	TMP or TMP+SMX	NR	9
Angelakis et al, 2013[24]	Retrospective cohort; France	2006–2011	46	17	Brucellosis	NR	NR	Throughout pregnancy	Variable (range 2 weeks – 6 months)	TMP+SMX	No	NR
Bailey et al, 1983[25]	RCT; New Zealand	1980–1982	44	44	Asymptomatic bacteriuria	NR	Either single dose CTX at 1.92g or 0.96g CTX BD (160 mg TM + 800mg SMX) for 5 days	<30 weeks gestation	Single dose or 5 days	TMP+SMX	No	No
Brumfitt & Pursell, 1973[26]	RCT; United Kingdom	1973	155	120 +35 referrals	Bacteriuria	0	NR	Only 10<16 weeks pregnant; 35 referrals exposed at time of conception	Unclear	TMP+SMX	NR	NR
Carcopino et al, 2007[27]	Retrospective cohort; France	1991–2005	53	22	Q fever	NR	320 mg TMP and 1600 mg SMX	Throughout pregnancy	Variable; mainly long-term >5 weeks	TMP+SMX	No	No
Colley et al, 1982[28]	Retrospective cohort; Australia	1978–1981	7371	209*	Unclear	0	NR (most given “normal dose”)	Throughout pregnancy	NR	TMP+SMX	NR	NR
Czeizel et al, 2001[29]	Case-control study; Hungary	1980–1996	61016	794	Respiratory and UTI	0	80 mg TMP + 400 mg SMX 2 tablets x 2/3 daily on day 1, then 1 tablet x 2/day	Throughout pregnancy	4 days	TMP+SMX	Various	Cases 50%
Denoeud-Ndam et al, 2014[43]	RCT; Benin	2009–2011	432	364	HIV (malaria prophylaxis)	432	160mg TMP + 800mg SMX	2nd and 3rd trimester	Throughout pregnancy	TMP+SMX	Mefloquine (one arm, n=146); mefloquine, quinine or arthemeter–lumefantrine in case of malaria, depending on symptoms and levels of parasitaemia; antiretroviral therapy (32.7% AZT/3TC/EFV, 23.6% AZT/3TC/NVP, 18.1%	5 mg folic acid (all)

Study	Design; setting	Reporting period	Overall study size	Numbers receiving CTX	Indication	HIV+	Dose	Timing	Duration	Main drug provided	Other drugs	Folate
											D4T/3TC/NVP, 15.7% D4T/3TC/EFV) D4T/3TC/NVP, 15.7% D4T/3TC/EFV)	
Dow et al, 2013[44]	RCT; Malawi	2004–2009	1236	768	HIV (malaria prophylaxis)	1236	160mg TMP + 800mg SMX BD	2nd and 3rd trimester	Throughout pregnancy	TMP+SMX	Antiretroviral therapy (225/768)	NR
Hernández-Díaz et al, 2000[30]	Case-control study; USA and Canada	1976–1998	15319	66**	UTI	0	NR	−1 to +3 lunar months	NR	TMP+SMX	Unclear	11% used daily peri-conceptional folic acid supplements
Hill et al, 1988[31]	Case-control study; United Kingdom	1983	791***	42	NR	NR	NR	3 months pre-conception & 1st trimester	NR	TMP+sulpha drugs	NR	Unclear
Jungman et al, 2001[32]	Retrospective cohort; United Kingdom	1994–1999	195	29	HIV (prophylaxis)	29	NR	1st Trimester	NR	TMP+SMX	No	NR
Khan et al, 2001[33]	Retrospective cohort; Saudi Arabia	1983–1995	92	40	Brucellosis	0	160mg TMP + 800mg SMX BD	Throughout pregnancy	>=4 weeks	TMP+SMX (23) TMP+SMX + rifampicin (17)	17 also received rifampicin	NR
Klement et al, 2014[45]	RCT; Togo	2009–2012	264	126 (number analysed)	HIV (malaria prophylaxis)	264	160mg TMP + 800mg SMX BD	2nd and 3rd trimester	Throughout pregnancy	TMP+SMX	300mg AZT or d4T, 3TC and NVP (depending on WHO Stage); malaria treatment where indicated	Yes (all)
Matok et al, 2009[34]****	Retrospective cohort; Israel	1998–2007	84823	346	“primarily” UTI	NR	NR	1st trimester	Mean 7.4 days for all DHRI	TMP+SMX	2 women methotrexate only, 1 sulfasalazine only	NR
Meijer et al, 2005[35]	Case-Control study; Netherlands	1997–2002	2217	15	Unclear	NR	NR	1st Trimester	Unclear	TMP	7 TMP only, 2 TMP +sulfoxamide, 3 sulfasalazine	~24% all cases and controls
Michigan Medicaid surveillance study, 2003[36]	Surveillance; USA	Unclear	2296	2296	Unclear	NR	NR	NR	NR	TMP+SMX	NR	NR
Roushan, et al 2011[37]	Retrospective case series; Iran	2000–2010	19	14	Brucellosis	NR	NR	Throughout pregnancy	2 months	TMP+SMX	Rifampicin (all women)	NR
Santos et al, 2011[38]	Case-control (prospectively collected data); Canada	1998–2003	63338	214	Unclear	NR	NR	Throughout pregnancy	Variable	TMP+SMX	NR	NR
Valentini et al, 2009[39]	Retrospective hospital case review; Italy	2009 (published)	76	76	Toxoplasmosis	NR	160mg TMP + 800mg SMX BD	2nd and 3rd trimester (Start at least after week 14, and stop 2 weeks before delivery)	Variable – up to 24 weeks	TMP+SMX	Spiramycin (all women)	Yes (all)
Walter et al, 2006[3]	Cohort nested within an RCT; Zambia	2001–2004	255	67	HIV (prophylaxis)	67	80mg TMP + 400mg SMX BD	Delayed until 2nd trimester	Ongoing; dependent on CD4	TMP+SMX	Chloroquine (2002) then sulfadoxine-pyrimethamine (2003) ART	800 mg (all women)

Study	Design; setting	Reporting period	Overall study size	Numbers receiving CTX	Indication	HIV+	Dose	Timing	Duration	Main drug provided	Other drugs	Folate
Wen et al, 2008[40]	Retrospective cohort; Canada	1980–2000	74807	DHRI: 11386 TMP-SMX: 12546	NR (any exposure but mostly UTI)	NR	NR	Pre-conception period and throughout pregnancy	NR	TMP+SMX	No	NR
Yaris et al, 2004[41]	Toxicology Information and Follow-up Service; Turkey	1999–2004	511	11	UTI	NR	TM-SMX 160–800 mg for 7–10 days (2 cases with Gentamicin)	1st trimester	7–10 days	TMP+SMX	Gentamicin in 2 cases	NR (unlikely)

CTX, cotrimoxazole; 3TC, lamivudine; ART, antiretroviral therapy; AZT, zidovudine; BD, twice daily; DHRI dihydrofolate reductase inhibitors; NR, not reported; NVP, nevirapine; RCT Randomised control trial; TMP+SMX, cotrimoxazole (TMP trimethoprim; SMX sulfamethoxizole); UTI, urinary tract infection

* 127 additional patients given sulfamethizole alone

** Trimethoprim, triamterene, and sulfasalazine. Exact numbers not given

*** Cases only

**** Includes fetal anomalies diagnosed via prenatal ultrasound

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Table 2

Congenital anomalies (Case control studies not included)

Study	Trimester	Number of live births to women receiving CTX (N=4196)	Number of infants with congenital anomaly (N=232)	Number of infants with neural tube congenital anomaly (N=32)	Type of anomaly (all reported)
Anderson et al, 2013[23]	T1	402	25*	1	Limb defects Urinary tract defects (UTD) Orofacial defects Cardiovascular defects (CVD) Neural tube defects (NTD)
Angelakis et al, 2013[24]	T1	5	0	0	--
Angelakis et al, 2013[24]	T2/3	8	1	0	Bilateral renal agenesis
Bailey et al, 1983[25]	T1/T2	43	0	0	--
Brumfitt & Pursell, 1973[26]	T1	10	0	0	--
Brumfitt & Pursell, 1973[26]	T1	35	0	0	--
Brumfitt & Pursell, 1973[26]	T2/3	110	4**		Cleft lip, hypospadias, Robin syndrome, extra digits All cases at T2
Carcopino et al, 2007[27]	NS	19	1	0	Potter's syndrome
Colley et al, 1982[28]	T1/2/3	209	8***	1	Patent ductus arteriosis Atrial septal defect Hypospadias Dislocated hip Metatarsus varus Cavernous haemangioma Other
Denoueud-Ndam et al, 2014[43]	T2/3	325	5****	0*****	Clubfoot Umbilical hernia Hydrocephaly
Jungman et al, 2001[32]	T1	29	1	1	NTD, hydrocephalus
Khan et al, 2001[33]	NS	40	0	0	--
Klement et al, 2014[45]	T2/3	117	1	0	Polydactyly
Matok et al, 2009[34]	T1	385	59	29	29 NTD 13 CVD 4 UTD
Michigan Medicaid surveillance study, 2003[36]	NS	2296	126	--	37 CVD
Roushan et al, 2011[37]	T1-3	9	0	0	--
Valentini et al, 2009[39]	T2/3	76	0	0	--

Study	Trimester	Number of live births to women receiving CTX (N=4196)	Number of infants with congenital anomaly (N=232)	Number of infants with neural tube congenital anomaly (N=32)	Type of anomaly (all reported)
Walter et al, 2006[3]	T2/3	67	1	NR	NR
Yaris et al, 2004[41]	T1	11	0	0	NR

CTX, cotrimoxazole; CVD, cardiovascular defects; G, gestation; NR, not reported; NTD, neural tube defects; T, trimester; UTD, urinary tract defects

* Only major malformations included

** All events were associated with T2 exposure

*** All events were associated with T2/3 exposure

**** An additional malformation was reported among a stillborn infant

***** There was one intra uterine fetal death diagnosed with encephalocele and ventral hernia