South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Obstetrics

EVIDENCE SUMMARY:

Date: 20 March 2011

Question: Is co-trimoxazole safe to use in pregnancy?

The effectiveness of co-trimoxazole (CTX) in reducing mortality has been established. In the pre-ART era, CTX prophylaxis reduced deaths by 48%; AHR 0.52 (0.37 - 0.89) in HIV-infected persons with CD4 counts < 200 cells/uL.[1] The survival benefit has remained consistent over time, and has also been shown for people taking antiretroviral therapy (ART). Recent data showed a 36% reduction in mortality in individuals on ART, that extended to CD4 counts of up to 350 cells/uL (AHR 0.64; 95% CI 0.57 - 0.72).[2]
The absolute risk reduction in death is considerable; 0.87 without CTX vs 0.92 with CTX.[2] These studies however, either excluded pregnant women, or their inclusion was not specified. It is therefore not known if pregnant women would benefit in the same way as non-pregnant adults. Several guidelines now recommend daily CTX prophylaxis for people, including pregnant women, with CD4 counts < 200 cells/uL, or with WHO stage II, III & stage IV disease.[3,4]

CTX prophylaxis may also reduce TB mortality regardless of HIV status, as well as mortality among family members in households of HIV-infected people.[5,6] In malaria-endemic areas CTX use results in a marked reduction in malaria during pregnancy (OR 0.43; 95% CI 0.19 - 0.97).[7]

Co-trimoxazole is an FDA category C drug: i.e. animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women.
How often CTX is used in HIV-infected pregnant women, is unknown. Clinician reluctance to use it may stem from concerns around infant hyperbilirubinaemia and kernicterus with 3rd trimester use, and teratogenicity following 1st trimester use.

Evidence of a "Co-trimoxazole in Pregnancy Registry" could not be sourced and the most recent systematic review of sulphonamides in pregnancy was reviewed.[8]
This review examined 43 papers on sulfonamides in pregnancy. Sixteen studies were case reports/case series, 5 were pharmacokinetic studies, 11 were case-control studies, 7 were cohort studies, and 4 were clinical trials. Most studies were done in 1930's, 50's, 60's and 70's. Only 4 studies were performed after 1990. Most of the studies were on the use of other sulfonamides for various indications, ranging from gonorrhoea, inflammatory bowel disease, endocarditis prophylaxis, to UTI's. Only 3 studies were on trimethoprim use, and 8 were on CTX (of which 2 were clinical trials).

The evidence for an association with hyperbilirubinaemia emanated exclusively from 5 case series (14/27), and for kernicterus (12/95) from a clinical trial wherein sulfisoxazole was given directly to premature neonates.
The data on safety, mainly from cohort and pharmacokinetic studies, showed no cases of kernicterus in 663 infants following antenatal or intrapartum sulfasalazine/sulfadiazine exposure.

Case-control analyses (n = 8174) of birth defects with 1st trimester trimethoprim and other dihydrofolate reductase inhibitors (not specified) showed a significant increase in cardiovascular defects (0.6%), oral clefts (0.5%), and neural tube defects (0.5%) versus control infants (0.1-0.2%). Dose and condition treated were not specified. In the only cohort study of 195 HIV-infected pregnant women, 3 out of 13 infants (23%) were born with birth defects after exposure to antiretrovirals, CTX, pyrimethamine and carbamezapine.

Two clinical trials (n = 164) and another case-control study (n = 6228) of CTX use in the 1st trimester didn't show any association with birth defects.

This review has several limitations, some already alluded to above. Different sulfonamides were included (a class-effect cannot be assumed), most women were not taking CTX as prophylaxis for PCP, the majority of studies were case reports or case-control studies, the study with the strongest association had a total of only 13 exposed infants, and no maternal outcomes were reported in any of the studies.

Notwithstanding the limitations, the lack of an association with kernicterus is reassuring. The absolute risk differences for birth defects are also extremely small (0.5%).

To address CTX safety, future reviews should ideally consider the following prerequisites:
1) cohort or randomized studies with CTX use stratified by dose and trimester
2) sufficient sample size to detect an increase in CTX-specific birth defects such as NTD's or facial cleft
3) evaluation of pregnant women at risk (HIV-infected women with CD4 counts < 200 cells/uL)
4) adjusting for folic acid use
5) adjusting for other variables including age, smoking, family history, co-morbid conditions, or use of other drugs
6) reporting on the absolute risks of birth defects or kernicterus on the one hand, versus maternal mortality or hospitalization for bacterial pneumonia or PCP on the other hand.

Pregnant women are generally excluded from experimental drug trials, in accordance with Helsinki.[9] This automatic exclusion criterion has been applied with such rigour, even when it is known that the drug in question doesn't cross the placenta.
Whilst well-intended, this exclusion may possibly have harmed rather than benefited pregnant women and their babies over the years. Drug use in pregnancy is guided by the results from animal reproduction studies, but has more recently been influenced by voluntary registries, post-marketing surveillance, isolated case reports, case-control studies, or (rarely) cohort studies.

Case reports or case-control studies are prone to several forms of bias. Cohort studies tend to perform a bit better. However, it takes about 15-20 years to complete a pregnancy registry. By the time it is completed and the drug (aspirin) is deemed safe,[10] a new drug (clopidogrel) is already in use. We simply cannot catch up with this approach. It is hardly surprising therefore that drugs used in pregnancy are either ancient (methyldopa, salbutamol), unsafe for the woman (nifedipine), or have disappeared from the market altogether (dihydrallazine, hexoprenaline).

Drug use in pregnancy is also largely informed by assignment of FDA category (A to X).
A - we know its safe (thyroxine is the only drug I'm aware of in this category)
B - we think its safe (amoxicillin, paracetamol, didanosine)
C - we think its unsafe (CTX, quinine, heparin, a long list)
D - we know its unsafe (warfarin, EFV, doxycycline)
X - don't ever use in pregnancy (ribavarin, leflunomide, misoprostol)

This FDA label does not consider whether the drug is indicated for treatment or prophylaxis, the lethality of the condition, the dose and duration, placental transfer and degradation, pharmacokinetics in the fetus, or use stratified by gestation.

As an example, during animal studies AZT was associated with vaginal squamous tumours in female rodents. In humans concerns about mitochondrial toxicity and hypospadias in infants following AZT use in pregnancy dominated the literature in the late 90's, and this issue remained largely unresolved.[11,12] Zidovudine is still an FDA category C drug, but sanity prevailed. The PACTG 076 trial and data from the Antiretroviral Pregnancy Registry (APR) weighed in favour of its continued use.[13,14]

Not too long ago, TDF use in pregnancy was considered unsafe and prohibited. Mice had developed liver adenomas after high doses of TDF, and monkeys got bone problems. The draft SA adult guidelines (2008) specifically recommended 3TC monotherapy (with d4T + LPV/r) for hepatitis B-positive pregnant women until delivery, and to start TDF postpartum. Similar international recommendations existed for TDF use in pregnancy 4 years ago.[15,16]

Recommendations for the care of HIV-infected pregnant women in need of lifelong ART, are generally based on expert opinion rather than evidence accrued from randomized studies conducted during pregnancy. Drug choices appear to be driven largely by medico-legal concerns and manufacturer's recommendations, rather than scientific data. STG's for HIV-infected pregnant women don't actually exist, like guidelines for "adults on renal replacement therapy", "internally displaced persons", or guidelines for children. Maternal health is placed under a "PMTCT" heading, reflecting perhaps the primary objective - that of infant HIV-1 transmission. The emphasis seems to be on PMTCT instead of maternal outcomes, although it is well known that infant survival is dependent on maternal health.[17]

Factors that guide the decision to subsequently use or not to use certain drugs (eg TDF, AZT) in pregnancy after initial concerns, are occasionally unclear, and appear to be driven by considerations other than science. The WHO has to be commended for disregarding the manufacturer's "black box warnings" on both EFV and NVP. It is difficult to understand why scientific data, even from observational cohort studies are not considered, given the difficulty with conducting RCT's in pregnancy. Ironically the largest randomized drug trial to date in obstetrics (n = 18 530) was with misoprostol.[18] This type of research is unlikely to be repeated, and the obstetric community has to shoulder the blame for this. Be that as it may be, observational cohort studies - as biased as they are - still provide better quality evidence than case reports or case-control studies.

Without wishing to re-ignite an endless debate around the above points, suffice to say the following: CTX prophylaxis should be promoted for use in HIV-infected pregnant women at risk, from the 2nd trimester onwards, in accordance with the current national guidelines.

Women of reproductive age who need CTX prophylaxis should continue to use it, together with folic acid supplementation. recommendation for or against the use of CTX in the 1st trimester cannot be made. The evidence linking 1st trimester CTX use with birth defects is extremely weak. On balance, the absolute risk of a maternal death without CTX appears substantially higher than the risk of a birth defect with CTX use.

Summary prepared by Dr E Bera

Affiliation: University of the Witwatersrand, Department of Obstetrics & Gynaecology; Adult Hospital Level Committee (2010-2012)

Conflicts of interest: None declared

References

1. Badri M, Ehrlich R, Wood R, Maartens G. Initiating co-trimoxazole prophylaxis in HIV-infected patients in Africa: an evaluation of the provisional WHO/UNAIDS recommendations. AIDS 2001; 15: 1143-1148.
2. Hoffmann CJ, Fielding KL, Sharalambous S, et al. Reducing mortality with cotrimoxazole preventive therapy at initiation of antiretroviral therapy in South Africa. AIDS 2010; 24: 1709-1716.
3. MMWR. Morbidity and mortality weekly report. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. April 10, 2009. Available at www.cdc.gov
4. Clinical guidelines for the management of HIV & AIDS in adults and adolescents. National Department of Health. South Africa 2010. Available at www.doh.gov.za
5. Grimwade K, Sturm AW, Nunn AJ, et al. Effectiveness of cotrimoxazole prophylaxis on mortality in adults with tuberculosis in rural South Africa. AIDS 2005; 19: 163-168.
6. Cotrimoxazole prophylaxis by HIV-infected persons in Uganda reduces morbidity and mortality among HIV-uninfected family members. AIDS 2005; 19: 1035-1042.
7. Kapito-Tembo A, Meshnick SR, van Hensbroek MB, et al. Marked reduction in prevalence of malaria parasitaemia in HIV-infected pregnant women taking cotrimoxazole with or without sulfadoxine-pyrimethamine intermittent preventive therapy during pregnancy in Malawi. J Inf Dis 2011; 203: 464-472.
8. Forna F, McConnell M, Kitabire FN, et al. Systematic review of the safety of trimethoprim-sulfamethoxazole for prophylaxis in HIV-infected pregnant women: implications for resource-limited settings. AIDS Reviews 2006; 8: 24-36.
9. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. June 1964. Helsinki, Finland.
10. Duley L, Henderson-Smart DJ, Meher S, King KF. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database of Systematic Reviews 2007, Issue 2.
11. Blanche S, Tardieu M, Rustin P, et al. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. Lancet 1999; 354: 1084-1089.
12. Watts DH, Li D, Handelsman E, et al. Assessment of birth defects according to maternal therapy in the Women and Infants Transmission Study. J Acquir Immune Defic Syndr 2007; 44: 299-305.
13. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. PACTG 076. N Engl J Med 1994; 331: 1173-1180.
14. Antiretroviral Pregnancy Registry Steering Committee. APR Interim report for 1 January 1989 - 31 January 2007. Wilmington, NC. Available at www.APRegistry.com
15. World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents. Recommendations for a public health approach. WHO. Geneva, Switzerland, 2006.
16. Public Health Service Task Force. Recommendations for use of antiretroviral drugs in pregnant HIV-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. Baltimore. November 2, 2007. Available at http://aidsinfo.nih.gov
17. Brahmbhatt H, Kigozi G, Wabwire-Mangen F, et al. Mortality in HIV-infected and uninfected children of HIV-infected and uninfected mothers in rural Uganda. J Acquir Immune Defic Syndr 2006; 41: 504-508.
18. Gulmezoglu AM, Villar J, Ngoc NN, et al. The WHO multicentre double-blind randomized controlled trial to evaluate the use of misoprostol in the management of the third stage of labour. Lancet 2001; 358: 689-695.