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Essay

New Medicines for Tropical Diseases in Pregnancy: Catch-22

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There were an estimated 536,000 maternal deaths in the world in 2005, of which 533,000 (99%) occurred in developing countries [1]. Maternal and perinatal conditions are a major contributor to the global burden of disease, yet the pipeline of new drugs specifically for maternal health is alarmingly small [2]. Only 17 drugs are under active development for maternal health indications—less than 3% of the pipeline in cardiovascular health. Since the disaster of thalidomide 50 years ago, the medical profession has been rightfully very cautious about giving newly developed drugs to pregnant women, for fear that they might damage the unborn baby. Particular caution has been exercised in the first trimester to avoid teratogenicity during organogenesis.

A Dangerous "Catch-22"

The result has been that newly introduced medicines often carry a prescribing caveat that they should not be used in pregnancy. There may have been no worrying results from reproductive toxicology testing to warrant this caution—simply insufficient clinical information in pregnancy. But for a new drug, there is never sufficient clinical information in pregnancy. Pregnant women with potentially fatal illnesses may be treated with inferior drugs to avoid a hypothetical risk to the unborn child (and the consequent liability).

Realising that this was a dangerous "Catch-22"—medicines not recommended therefore not prescribed—not prescribed therefore no information—regulatory authorities in developed countries have begun to encourage pharmaceutical companies to gather information on the use of new drugs in pregnancy. In tropical countries, where infectious diseases account for half of all deaths, and 99% of maternal deaths occur, the treatment of infections in pregnancy is particularly problematic. There are few or no studies in pregnancy on most drugs used for the treatment of tropical infections, and so few or no evidence-based recommendations.

Essays articulate a specific perspective on a topic of broad interest to scientists.

Malaria in Pregnancy

Malaria, the most important parasitic infection of humans, illustrates this problem well. Malaria infects about 5% of the world's population at any time, and is a particular problem in pregnancy. There is a renewed international interest in the infection, and malaria in pregnancy is rightly considered a priority area. Malaria in pregnancy reduces birth weight (and thereby infant survival). In low-transmission areas there is an increased risk of severe falciparum malaria and consequent death of both mother and foetus [3]. The health community has finally realised that even if the mother is asymptomatic, the presence of malaria parasites in the blood is always harmful to the foetus and must be treated promptly and effectively.

But treated with what? There have been remarkably few studies of antimalarial drugs in pregnancy. Of over 500 antimalarial drug trials conducted between 1966 and December 2006, only 31 evaluated antimalarial treatments (including intermittent preventive treatments) specifically in pregnant women (and 14 of these were from a single centre) [4]. Only primaquine and tetracyclines are considered contraindicated in pregnancy, although the evidence base for the safety of widely used antimalarials such as amodiaquine is weak [5], and recommended dose regimens for pregnant women are all derived from studies in non-pregnant adults.

Drug regimens should be recommended on the basis of pharmacokinetic and pharmacodynamic information in the target population. Where blood or plasma concentrations of the antimalarial drugs have been measured in late pregnancy, they have usually been found to be reduced [6,7]. For artemether, dihydroartemisinin, atovaquone, proguanil, and lumefantrine, the reductions have been substantial, and likely to have contributed to poor therapeutic responses, yet there have been no studies of higher dose regimens in pregnancy. In recent years, sulfadoxine–pyrimethamine (SP) replaced chloroquine as the most widely used antimalarial drug in pregnancy. However, the pharmacokinetic properties of sulfadoxine and pyrimethamine in pregnancy have only just been reported, years after the policy recommendations and widespread deployment of SP first as a treatment and later as intermittent preventive treatment in pregnancy. Blood concentrations of sulfadoxine were found to be 40% lower during pregnancy compared with after pregnancy [8], suggesting that the dose of SP in pregnancy may have been too low.

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Abbreviations: SP, sulfadoxine–pyrimethamine

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Safety of Artemisinin Derivatives in Pregnancy

The safety of the artemisinin derivatives in early pregnancy remains uncertain, as these drugs are embryotoxic in animals [9,10]. They are not recommended for uncomplicated malaria in the first trimester, unless effective alternatives are unavailable.

There is now a reasonable body of evidence for safety from clinical trials in nearly 1,000 women in the second and third trimesters of pregnancy, and artemisinin-based combination treatments are now recommended treatments in the second and third trimesters [6]. Severe malaria in late pregnancy carries a mortality approaching 50%—approximately 2.5 times higher than in non-pregnant patients. Artesunate has been shown to reduce the mortality of severe malaria by 35% compared with quinine, and, unlike quinine [11], it does not cause severe recurrent hyperinsulinaemic hypoglycaemia, for which pregnant women are at considerably increased risk. But quinine is still the most widely used treatment for severe malaria in pregnancy. Somehow, the unknown, but certainly very small, risk to the foetus posed by artesunate is considered to exceed the 35% increased risk of both mother and baby dying from malaria. Although artesunate is clearly now the drug of choice in severe malaria, there have been no pharmacokinetic studies in pregnant women to guide dosage. By extrapolation from studies in uncomplicated malaria, the currently recommended dose could again be too low.

We Need Evidence to Inform Practice

What is needed now is evidence. Industry is usually reluctant to underwrite studies of new drugs in pregnant women [2], particularly in the tropics. Research centres need to be encouraged to study the treatment of infections in pregnancy. There is now active research on HIV, malaria, and helminth infections in pregnancy, but not for other tropical infections. For antimalarial, antitrypanosomal, and antileishmanial drugs, the pharmaceutical industry's role in drug development will be increasingly assumed by public–private partnerships such as the Medicines for Malaria Venture and the Drugs for Neglected Diseases Initiative. International agencies and funders need to provide adequate support for quality studies in pregnancy and, in an increasingly litigious climate, to underwrite the liabilities. Pregnancy registries should be established to facilitate systematic recording of adverse effects on the newborn, and assessment of the neurological development of infants until at least one year of age, and preferably longer.

These are long-term investments. Unfortunately, reliable diagnostic facilities for malaria, or even birth records, are difficult to find in the parts of the world where these registries need to be established. Particular efforts should be made to document first-trimester exposures accurately to assess teratogenicity risks. This documentation could be achieved most reliably in specific centres where pregnant women attend antenatal clinics in the first trimester.

Research ethics review boards have difficult jobs, and tend to err on the side of caution (i.e., negativity) when confronted with applications to study new drugs or drug regimens in pregnant women. In assessing the risks and benefits, research ethics review boards also need to consider the risks of our continued ignorance of how best to treat serious infectious diseases in pregnancy, and the benefits to the mother and her baby of appropriate treatment. Protagonists always demand urgent action, but amongst many priorities, optimising the dose of existing anti-infective treatments in late pregnancy must be near the top. Such optimisation means assessing the pharmacokinetic properties of systemic anti-infective drugs in late pregnancy, and where blood concentrations are found to be reduced significantly, evaluating higher doses. Unfortunately, capacity for drug measurement is woefully lacking in tropical countries, so this too needs to be strengthened [12].

Conclusion

"Better safe than sorry" is the mantra of our risk-averse age, and there are few more challenging areas of drug development than establishing drug safety in pregnancy. Add to this the difficulties in conducting clinical trials and pharmacokinetic studies in pregnancy in most tropical countries, and it is not difficult to understand our current state of ignorance. We do not know how best to treat most tropical infectious diseases in pregnancy. It is a difficult problem, but one that should no longer be ignored. ■

References

1. World Health Organization (2007) Maternal mortality in 2005. Estimates developed by WHO, UNICEF, UNFPA and the World Bank. Available: http://www.who.int/reproductive-health/publications/maternal_mortality_2005/mme_2005.pdf. Accessed 8 May 2008.
2. Fisk NM, Atun R (2008) Market failure and the poverty of new drugs in maternal health. PLoS Med 5: e22. doi:10.1371/journal.pmed.0050022
3. Desai M, ter Kuile FO, Nosten F, McGready R, Asamoa K, et al. (2007) Epidemiology and burden of malaria in pregnancy. Lancet Infect Dis 7: 93-104.
4. Myint HY, Tipmanee P, Nosten F, Day NP, Pukrittayakamee S, et al. (2004) A systematic overview of published antimalarial drug trials. Trans R Soc Trop Med Hyg 98: 73-81.
5. Tagbor HK, Chandramohan D, Greenwood B (2007) The safety of amodiaquine use in pregnant women. Expert Opin Drug Saf 6: 631-635.
6. Ward SA, Sevene EJ, Hastings IM, Nosten F, McGready R (2007) Antimalarial drugs and pregnancy: safety, pharmacokinetics, and pharmacovigilance. Lancet Infect Dis 7: 136-144.
7. Barnes K, Watkins WM, White NJ (2008) Antimalarial dosing regimens and drug resistance. Trends Parasitol 4: 127-134
8. Green MD, van Eijk AM, van Ter Kuile FO, Ayisi JG, Parise ME, et al. (2007). Pharmacokinetics of sulfadoxine-pyrimethamine in HIV-infected and uninfected pregnant women in Western Kenya. J Infect Dis.196: 1403-1408.
9. China Cooperative Research Group on qinghaosu and its derivatives as antimalarials (1982) Studies on the toxicity of qinghaosu and its derivatives. J Tradit Chin Med 2: 31-38.
10. Longo M, Zanoncelli S, Manera D, Brughera M, Colombo P, et al. (2006) Effects of the antimalarial drug dihydroartemisinin (DHA) on rat embryos in vitro. Reprod Toxicol 21: 83-93.
11. Dondorp A, Nosten F, Stepniewska K, Day N, White NJ, et al. (2005) Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. Lancet 366: 717-725.
12. Barnes KI, Lindegardh N, Ogundahunsi O, Olliaro P, Plowe CV, et al. (2007) World Antimalarial Resistance Network (WARN) IV: Clinical pharmacology. Malar J 6: 122.