

Perinatal Infections – Problems in Developing Countries

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This paper was presented at the *Perinatal Infections* symposium at the 3rd World Congress of Perinatal Medicine held in San Francisco, USA, on 22 October 1996.

ABSTRACT

The transmission of infections from the biologic mother to her offspring is popularly known as perinatal infection (PI). It is not synonymous to infections during the perinatal or neonatal period. Physicians should avoid focusing attention only on the TORCH agents in the evaluation of suspected PI. Perinatal period begins from 28 weeks of gestation. Would one consider *in utero* infections in the first or second trimester of pregnancy as PIs?

Developing countries have difficulty in collecting reliable and accurate data of PIs. These data are useful to define the magnitude of the problems, to monitor the trends, to recognise the mode of spread, and to find a solution of PIs.

Most PIs are asymptomatic and diagnosis is extremely difficult. Developing countries need rapid, easy-to-operate, simple, and cheap diagnostic tools urgently. Access to health care in the remote city is limited. Newer drugs are too expensive and very few patients can benefit from these.

Each developing country should prioritise its PI problems and tackle those that have serious public health problems and socio-economic impact. Most developing countries should focus on HIV (human immunodeficiency virus) and HBV (hepatitis B virus) infections. Other countries where ophthalmia, malaria or tuberculosis are prevalent or endemic, should focus on these.

Developing countries are more willing to allocate the budget for prevention of diseases than for treatment. There may be problem of promulgating the information on prevention of diseases because of illiteracy, multi-lingual community.

Vaccines where available, should be affordable. Other effective prevention guidelines should be workable in poorer nations. The government should play an important role in enforcing immunisation program by intensive promotion program or by legislation.

Keywords: HIV(human immunodeficiency virus), HBV(hepatitis B virus) infections, maternal-fetal infection, ophthalmia, screening tests

Definitions of perinatal infection

The transmission of infections from the biologic mother to her baby is known as perinatal infection

(PI). Infections, eg. tetanus neonatorum, developed in the perinatal period are not PIs. Strictly, infections such as rubella, acquired before 28 weeks of gestation are also not PIs. Some considered PIs when the infant was infected from the mother's genital tract during birth process. The pathogenic organisms include chlamydia, gonorrhoea, hepatitis B, herpes simplex, etc.

The TORCH acronym that is popularly used can narrow the physician's outlook in the diagnosis of PIs. (T=toxoplasmosis, R=rubella, C=cytomegalovirus, H=herpes simplex virus). Most people would focus on these biologic agents only when considering PIs. Other pathogens such as Group B streptococcus, Parvovirus B19 and Epstein-Barr viruses can cause PIs. PI accounts for the majority of cases of HIV infection in children. Three quarters of AIDS cases in children under age 13 result from perinatal transmission.

Other terms have been used, or used interchangeably, to describe the mode of transmission of infection. These are: intrauterine infection, vertical transmission, congenital infections, congenital chronic infections, fetal infection, chronic fetal infections. The terminology "maternal-fetal infection" is more appropriate.

Priority of the problems in perinatal infections

With limited resources, a developing country should know its own PI problems that need to be tackled urgently. The priority, magnitude or the extent of the problems, the trends of the PIs, the modes of infection are helpful in formulation and implementation of specific control measures.

Each country should focus on PIs that have critical public health and serious socio-economic impact. Perinatal transmission provides a continuous source of HIV and HBV carriers in the developing countries. Prevention and control of these infections that are also global problems are of paramount importance. For countries where ophthalmia neonatorum, malaria, and tuberculosis are prevalent or endemic, these should also receive attention.

HIV infects a larger number of younger people resulting in loss of productivity from the work force, as well as family income. The orphans would have a multitude of problems following early deaths of the parents. At the 11th International Conference of AIDS held in Vancouver, Canada in

June 1996, it was projected that the number of people with HIV worldwide is expected to double by the year 2000. HIV infection in Asia will outstrip even that in Africa⁽¹⁾. Perinatal AIDS grows rapidly and women represent the fastest-growing population of new HIV infections. About 30% – 35% of the pregnant women transmit the HIV to their children. Thailand reported that 15% of the newborn babies are infected by HIV.

Hepatitis B virus is a major health problem throughout the world. There is a strong relationship, based on geographical correlation, case-control studies, between the incidence of primary hepatocellular carcinoma and the prevalence of the HbsAg carrier.

In Singapore, the prevalence of HBV infection increased from 9.3% in those below 5 years of age, to 54.6% in adults 10 years ago⁽²⁾. China has 120 million hepatitis B carriers, 40% of them are pregnant women. Each year, about 150,000 people die of hepatitis B in China. In Indonesia, 1 in 10 babies are born to mothers with hepatitis B. Thailand reported approximately 4 million hepatitis B carriers, a quarter of these acquired the disease perinatally.

Gonorrhoeal infection among pregnant women is a significant public health problem in South and Southeast Asia and the Pacific. The prevalence ranges from less than 1% in Malaysia to 12% in Thailand and Cameroon.

Although there are 300 – 500 million cases of malaria per year in the world, apparent congenital malaria is rare in areas in which malaria is endemic and levels of maternal immunity are high.

Diagnosis of perinatal infections

Reliable or accurate diagnosis of PIs is often difficult. Most PIs are subclinical, remain unnoticed for many years. Many disorders require sophisticated or costly laboratory detection techniques that are not available in the developing countries. Developing countries need rapid, cheap and easy-to-use diagnostic tools. There will be greater difficulty if the diagnostic tests require highly skilled, well-trained personnel to perform.

Few people in Africa are tested for HIV infection because the tests are not widely available. Those who have been tested tend to have come mainly from high-risk groups (eg. patients with sexually transmitted diseases or prostitutes, etc.), hence a selection bias. The test results cannot be reliably extrapolated to the general population. HIV tests by using the ELISA profile can be unreliable. ELISA method tends to show false positive results in people with a history of malaria, tuberculosis, and/or parasitic infections.

The Program for Appropriate Technology in Health (PATH), a non-profit, non-governmental, international organisation with its headquarters in Seattle, Washington has done greatly to improve the maternal and child health in the developing countries. PATH has focused on enhancing the appropriateness, effectiveness, safety, availability, and delivery of technologies for health. These technologies include

equipment, drugs, devices, vaccines, and procedures used to prevent, diagnose, and treat illness and to meet health needs. They also include the systems used to deliver health care and the methods used to disseminate information on health topics.

One of the most advanced diagnostics is the rapid, inexpensive HIV dipstick, developed to screen blood supplies. Several million HIV dipsticks have been used to screen blood supplies and diagnose patients throughout the world. It is not dependent on costly equipment, instrument, or supplies and can be read visually in 30 minutes. It is stable without refrigeration for up to six months. The manufacturing technology for the dipstick has been transferred to India, Indonesia, Singapore, and Thailand⁽³⁾.

The very vast majority of the inhabitants of the developing or third world countries live in rural areas. Access to health care including prenatal care in the cities can be limited. Science and technologies have not reached all areas. To be seen by a physician means forgoing one to two days' income, long distance travel using primitive sea and land transport, paying for expensive food and accommodation while in the city.

Screening

The Centers for Disease Control (CDC) recommended early HIV testing for pregnant women belonging to the high risk categories. They are informed the meaning of the results, indications to seek medical consultations, notification of the partners, and availability of community resources, etc. Such testing is beneficial to the individual and a primary means of preventing and decreasing maternal-fetal HIV transmission, a public measure to help control the HIV pandemic.

Screening for HIV infection should be performed with informed consent and adequate pre-test and post-test counselling. However, testing of high risk patients alone have missed > 50% of HIV positive women. More and more people advocate HIV testing for all pregnant women regardless of risk factors⁽⁴⁾. Recently the CDC called for routine HIV counselling and voluntary testing for all pregnant women⁽⁵⁾.

Screening of pregnant women for HBsAg is widely recommended. Early detection of HBsAg in pregnant women can help prevent infection in the newborn. The screening test is very costly if performed on large numbers of women. Each test costs about US\$10 – \$20. The most important challenge is the availability of simple, safe, effective products that address priority needs. Universal HBV vaccination of newborns however may be a more practical strategy than prenatal screening.

Routine screening for gonorrhoea in the general population in developing countries is not possible. Even in the developed countries, the Canadian Task Force advised against routine screening for gonorrhoea in the general population. It did recommend screening for high risk women and pregnant women.

Data collections of perinatal infections

The 1991 WHO resolutions had emphasised information as a vehicle for reaching "Health for All". One of the greatest problems faced by many developing countries is the unavailability of reliable data. Some figures did not have means to verify and the source of information can sometimes be conflicting. In the absence of reliable data, the Western press provide the figures such as AIDS, which are misleading.

Each developing country should therefore establish its own data collection system. A proper system enables the country to monitor the trends and mode of spread of a particular PI. All relevant data should be centralised to the main centre, to ensure reliability of the information. Where data about the particular PI are available, from the results coming from clinical and epidemiological studies, accurate and speedy statistical analyses are possible. Prompt decision making can then be facilitated.

One possible method of capturing all the cases is to make the specific PIs notifiable to enable epidemiological studies. Where possible, sero-epidemiological surveys should be done to see the actual extent of the specific infection in the population. Frequent revision of the case definitions of PI would render interpretation of the disease more difficult.

An electronic information system can be useful in supporting regional and global collaborative research, including discussion of research findings and expert advice over the information network. By doing so, technology transfer is made possible. An additional advantage is the availability of electronic library service and journal and references search. Acquisition and analysis of statistical data, and computing-aided training are also possible. Many developing countries are short of trained personnel for diagnosis and patient care and such computerised, distance-learning system would help greatly.

Most importantly, accurate and up-to-date information of certain PIs such as HIV and HBV are made available to the public. People can ask questions and use the system as a forum. Knowledge such as HIV infection can then be exchanged and shared.

Low cost drug treatment

Access and cost of the drugs for PIs are the major obstacle to the Third World. A course of zidovudine for the treatment of HIV infection, estimated to be US\$ 20,000.00 annually, is many months' income of an average person⁽⁶⁾. Developing countries charged that industrialised nations were focusing on research into costly drugs at the expense of the world's poor. These drugs are hopelessly out of reach for the vast majority of AIDS sufferers in the Third World, where 90% of the world's 22 million HIV-infected live. Many centres even reject the offer of drugs from research workers and drug companies for clinical trials unless they agree to provide low cost or free drug after completion of the drug trial. A number of studies are underway,

several focusing on shorter courses of zidovudine, trying other anti-viral drugs, or to find some form of intermittent therapy. It is also hoped that the price of the drug will fall with improved technology, economies of scale and competition, though such drug therapy is unlikely ever to be cheap.

Antiretroviral drugs combined with a protease inhibitor can reduce viremia in a sustained manner and delay development of drug resistance, without significant increase in toxicity. A significant fraction of HIV-infected patients at all stages of HIV infection have benefited and improved. However, would this new therapy push the cost of treatment even higher?

There is always a likelihood that patients do not comply with the physician's instruction in taking these expensive drugs. They may on their own initiative, reduce the dosage of the drugs or take the drugs less frequently, in order to save a few dollars. Sadly, taking the drugs irregularly could be disastrous. There is a danger of development and spreading of new resistant strains.

Neonatal gonococcal conjunctivitis (ophthalmia neonatorum) continues to cause blindness because the prophylactic agents are not completely effective and not widely available in many parts of the world. These agents are: 1% silver nitrate solution, erythromycin 0.5% eye ointment, and tetracycline 1% eye ointment. There are reports indicating bacterial resistance and toxicity. The cost of each bottle or tube of the agents is US\$ 7.30, 31 cents and 74 cents respectively. A recent study in Kenya found that povidone-iodine eye solution is an effective agent with broad antibacterial and antiviral activity to which no bacteria are known to be resistant. It is far less expensive and less toxic than the agents currently used to prevent neonatal conjunctivitis. A vial of povidone-iodine eye solution 2.5% costs only 10 cents (US). It is also more effective against *Chlamydia trachoma*⁽⁷⁾.

Prevention

Until a cure is found, prevention is the most important weapon in combating diseases such as HIV infection. A safe and efficacious vaccine for the specific disease is the most valuable tool to break the chain of perinatal transmission by eliminating the carriers.

Other prevention and control measures include sanitary precaution, education on good personal hygiene. Routine screening of blood donors, sterilisation of medical equipment, and use of disposable needles and syringes, etc are important. Family members should avoid sharing toothbrushes, towels, razors, combs, etc.

The government should play a key role in the prevention of PIs. There should be a national programme for the specific disease. It can work in partnership with various organisations such as the WHO, NGOs (non-governmental organisations), academic institutions, the health department, the corporate sectors, philanthropic foundations, as well as many other community-based groups.

Immunisation and vaccination

PATH is committed to increase access to and use of safe and effective vaccines. It endeavours to broaden the range of vaccination and vaccine delivery system, available in developing countries. The WHO has designated PATH a collaborating centre for AIDS and hepatitis B vaccination. PATH provides technical expertise in these areas to WHO and to national health authorities.

The developing countries denounced the lack of progress in creating an AIDS vaccine⁽¹⁾. AIDS research workers expressed frustration that no AIDS vaccine has been deemed worthy of large scale human testing despite more than a decade of research. The industrialised countries have opted to wait until experimental vaccines are refined to the point that they work in the large majority of test subjects. Poor nations are desperate and want to push forward with large scale testing if experimental vaccines show promise of protecting just a fraction of the AIDS-infected.

Many scientists warned that rushing ahead with newly developed vaccines poses enormous ethical and health risks. Offering a vaccine with only partial protection might lull people into thinking that they do not need to practise safe sex or avoid other high risk activities. Imperfect vaccines would be better than none at all. Scientists are for a safe and effective vaccine. About three dozen HIV vaccines are being investigated in small-scale clinical trials around the world. Some have succeeded in provoking immune response but critical gaps remain in the researchers' knowledge. It was also noted that all spending on vaccine research has been targeted at the strains of HIV found in industrialised countries. Less than US\$5 million a year is being spent world-wide to develop vaccines specifically for poor nations⁽¹⁾.

Immunisation of newborns against hepatitis B is now carried out in more than 40 developing countries⁽³⁾. In response to a call from WHO to halt the spread of this dreaded disease, the Indonesian government launched an immunisation campaign in 1996 in 10 provinces where the prevalence of hepatitis B is highest. It will produce 10 million vaccines annually, expanding to 15 million later.

The International Task Force on Hepatitis B immunisation has contributed greatly in lowering the cost of hepatitis B vaccine, to ensure that newborns in many countries will have access to the vaccine. In 1992, the World Health Assembly endorsed the recommendation that hepatitis B vaccination be extended to all of the world's infant by 1997. The primary objective of the expanded program on immunisation (EPI), sustained by the WHO, is to integrate hepatitis B vaccination into national infant immunisation programmes. A quadrivalent DTP-HB vaccine that combines diphtheria-tetanus-pertussis (DTP) vaccine with hepatitis B vaccine is introduced. Immunisation of children in infancy is the most cost-effective way to provide protection against hepatitis B, which is a leading cause of adult liver cancer.

In a developing country, distance is an important deciding factor in patient's compliance to complete the course of vaccination. Even the accelerated vaccination schedule of 0, 1, 2 months of hepatitis B, which resulted in the more rapid development of seroprotective concentrations of antibody, is not practicable in developing countries. Though the Chinese central government has planned to immunise all the children in China, unfortunately 70% of the children from the rural area and 15% from the urban areas did not receive immunisation in the stipulated time.

Our national childhood hepatitis B immunisation programme to prevent both perinatal and horizontal transmissions of HBV infection has been successful. Eighty-five percent, 91% and 94% of the Singapore infants were immunised in 1993, 1994 and 1995 respectively.

Hepatitis B vaccine can be costly. The additional costs of storage, transport, as well as syringes and needles will overburden the tight health budgets. Most countries including Singapore subsidise the cost of HBV immunisation. A clinical trial on reduced dose of HB vaccine was conducted in Singapore. The dosage was as immunogenic and efficacious as the standard dose⁽⁸⁾. The use of a lower dose of vaccine would reduce considerably the cost of the national immunisation programmes.

Public Health Education

Effective dissemination of information, education, and communication (IEC) on HIV or HBV is necessary in combating these dreadful infections. This should be made available to the general public through the mass media.

Where resources are limited, money for educational programme related to safe sex, use of condoms, as well as sexually transmitted diseases programme should be provided. Many developing countries include prevention of AIDS in the school curriculum. HIV prevention campaign in Thailand produced dramatic reduction in HIV infections.

Unfortunately, it is not easy to get across the published message on health education in developing countries, where the people speak different languages or dialects, and read and write different languages. There are about 40 major Indian languages, 13 of these appear on the Indian currency notes. In order to reach out to these people, IEC materials have to be translated, or prepared in the form of pictorial or audio-visual materials. These incur more finances and manpower. Also, the illiteracy rate is very high in developing countries.

Government efforts to fight the HIV disease are also hindered by taboos and cultural prejudices. Many countries denied the vulnerability of their population to the pandemic because of a misconception that it is a "decadent" foreign disease. There may also be cultural, traditional or religious resistance to topics on sex; eg. in Zambia, childless women are outcasts.

ACKNOWLEDGMENTS

The author wishes to thank Dr Goh Kee Tai, Head, Quarantine & Epidemiology Department, Ministry of the Environment, Singapore for his invaluable advise and also Dr S Sivasankaran for his help in preparing this paper.

REFERENCES

1. Laurence J. Abstracts and comments from the XI International Conference on AIDS. 1996:Supp A New York, SCP Communications, Inc. The AIDS Reader. New York
2. Goh KT. Hepatitis B virus infection in Singapore: Epidemiology, prevention and control. In: Oon CJ, Aw SE, Goh KT editors. Selected papers from the international symposium on viral hepatitis and hepatocellular carcinoma research, Singapore. The Department of Clinical Research, Singapore General Hospital, Singapore 1994:62-80.
3. Perkin GW. Improving the health of women and children in developing countries. Program for appropriate technology in health (PATH). Seattle, USA, 1993.
4. Segal AI. Physician attitudes towards human immunodeficiency virus testing in pregnancy. *Am J Obstet Gynecol* 1996; 174:1750-6.
5. Centers for Disease Control and Prevention. United States Public Health Service recommendations for HIV counselling and voluntary testing for pregnant women. *MMWR Morb Mortal Wkly Rep* 1995; 44:8-11.
6. Mauskopf JA, Paul JE, Wichman DS, White AD, Tilson HH. Economic impact of treatment of HIV-positive pregnant women and their newborns with zidovudine. Implications for HIV screening. *JAMA* 1996; 276:132-8.
7. Isenberg SJ, Apt L, Wood M. A controlled trial of povidone-iodine as prophylaxis against ophthalmia neonatorum. *N Engl J Med* 1995; 332:562-6.
8. Quarantine & Epidemiology Department, Ministry of Environment Singapore. Long-term immunogenicity and efficacy of a reduced dose of yeast-derived hepatitis B vaccine in children. *Epidemiological News Bulletin* 1996; 22:7-10.

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