Perinatal research in developing countries — Is it possible?

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Summary Maternal mortality remains the health statistic for which there is the greatest disparity between developing and developed countries. The risk of stillbirth or neonatal death is also high in developing countries. The inequality of research funding between rich and poor countries is dramatic, with only 10% of research funding directed towards diseases which contribute 90% of the global burden of disease. The need for high-quality, relevant perinatal research in developing countries is compelling. There are many examples of good perinatal research in developing countries. Nevertheless, significant challenges remain and are being tackled. We need better information about maternal and perinatal health, and about performance of the health services, we need more evaluation of what helps and what harms within the existing health services, and we need improved strategies for implementation of research findings.

Introduction

The inequalities in health between rich and poor countries are well documented. People who live in the rich, developed countries—predominantly in the northern hemisphere—have far healthier and longer lives than those who live in the poor, developing countries, predominantly in the southern hemisphere. These inequalities in health are particularly stark for maternal and child health.

Maternal mortality remains the health statistic for which there is the greatest disparity between developing and developed countries.1,2 An estimated 529,000 women die each year of pregnancy-related causes.2 More than 99% of these deaths occur in developing countries, where a woman has an average lifetime risk of dying from pregnancy-related conditions that is about 250 times greater than a woman in most developed countries.2 Morbidity associated with pregnancy and childbirth is less well documented, particularly...
in developing countries. Nevertheless, the World Health Organization (WHO) estimates that 30 million women develop complications following pregnancy each year. Mortality for children in developing countries is also high, especially at birth and during the first few weeks after birth. Each year 3.3 million babies are stillborn and 4 million die within 28 days of birth.2

None of this is new, but it has not always been considered newsworthy. The recent World Health Report2 outlines how for centuries the care of mothers and young children was regarded as a domestic affair, the realm of mothers and midwives. In the 20th century this purely domestic concern was transformed into a public health priority, first in the rich countries but eventually also in poor countries. This process culminated in the Millennium Development Goals, which included targets for reducing child mortality and maternal mortality as goals 4 and 5.

Research is a vital tool for identifying and tackling health problems. The inequity of research funding between rich and poor countries is dramatic. Only 10% of the US$50–60 billion spent annually on health research worldwide is directed towards diseases which contribute 90% of the global burden of disease.3,4 Identifying and removing the barriers to research in the developing world is crucial if this balance is to be redressed. Over the next 50 years it is anticipated that 97% of the world’s population growth will be in developing countries. If the world is to see the maximum benefit from health research, then the balance of research between the developed and developing countries needs a substantial shift. Worse still is that most of the research conducted in poor countries may be of little, if any, relevance to the people who live there, as it is primarily intended to benefit those who live in rich countries.3 Such research may be undertaken in the developing world because the disease prevalence is higher (as with AIDS, for example), because ethical constraints are less, or because the cost of doing the research is lower.

If clinicians and policy makers in low- and middle-income countries are to make best use of the health-care resources available to them, they require high-quality relevant evidence to inform their decision-making. They need good research that will improve their understanding of the clinical problems they face and help provide practical solutions. Such research should be conducted in a setting comparable to their existing health services. Once completed, it also has to be published, and then made accessible. There are many barriers to this process in developing countries. These include medical schools and hospitals being in disarray, shortage of money, poor salaries and career structures for academics, lack of local training and mentoring, no local journal for publication, and little guidance on how to write research papers.3

The need for perinatal research in developing countries is compelling. Such research needs to address the problems of maternal and neonatal health in a way that is both relevant to the communities and health services of these countries and scientifically robust. We believe such research is possible; much has already been achieved, but much more is still needed. In this chapter we will discuss some of the issues facing perinatal researchers in developing countries, present a range of examples that demonstrate what has been achieved to date, and discuss some of the challenges for the future.

Describing maternal and neonatal morbidity and mortality in developing countries

Reliable data on morbidity and mortality are often taken for granted in developed countries, yet in many developing countries such information is scant, at best. This lack of information may obscure huge health problems and hamper their being tackled. For example, births and deaths are not routinely registered in many developing countries. Cause of death is recorded in only 100 countries of the world, covering one-third of the world’s population. Our understanding of what is happening elsewhere has been enhanced by developing appropriate survey methods, often using indirect methods, and statistical modelling techniques. For 62 developing countries, representing 27% of the world’s births, the only estimates of maternal mortality are based on statistical modelling.2

For many developing countries, the lack of up-to-date, reliable information for planning and evaluation of maternal and neonatal health-care is among the major challenges faced by programme managers, health practitioners and health policy-makers. This lack of information is also a major handicap in the conduct of relevant research and the implementation of evidence-based decision-making. The gap between evidence of effectiveness and clinical practice is well known. Often routine care is not evidence-based, and the elimination of harmful or useless procedures faces strong resistance.6 Efforts to improve health practice are restricted by lack of data or poor-quality data. Reliable information is needed to estimate the burden of disease or ill-health, to help guide resource allocation and service planning, and to support health policy planning, implementation and evaluation. Improved understanding in all these areas will also facilitate the design and conduct of research relevant to the needs of developing countries.

The WHO Global Data System for monitoring maternal and perinatal outcome is one strategy for overcoming some of these barriers. This began with systematic reviews summarizing the available data on the effectiveness of interventions in the perinatal period in developing countries, and on the incidence and prevalence of maternal ill health.6,7 A simple data collection system was then developed with the aim of providing locally relevant data to maternal and neonatal health programmes and institutions. This system builds on existing information about maternal and perinatal outcome, and about the functioning and provision of care. The aim is to provide information that will help to improve decision-making and facilitate best practice. This Global Data System utilizes a network of institutions to conduct a series of simple short surveys on specific topics of global relevance. Surveys take place about every 2 years, and each is conducted within a randomly selected sample of the network (cluster survey).

The first survey was conducted in 2004, and focused on assessing the relationship between mode of delivery and maternal and perinatal outcomes among women giving birth in health facilities. It included all women delivering at selected health facilities in Africa and America during
The challenges of research in developing countries

Conducting high-quality research anywhere in the world is challenging, but as outlined above the barriers are greatest in the developing world. Many of the problems encountered by researchers in the developing world are similar to—albeit more extreme than—those in the developed world. So, for example, securing funding is an issue for all research, but is a far greater barrier in poor countries than rich ones. Long-term follow-up is never easy, but is particularly difficult in poor countries where the population may be mobile, literacy is low and there are no routine systems for recording births and deaths. Other problems are specific to developing countries: for example, deciding whether it is appropriate to use a placebo, or no treatment, for the control group of a randomized trial in situations where active treatment is known to be effective, but is not available locally and is unlikely to be so outside of the research project.

For the topic addressed within a trial to be relevant to the community within which it is being conducted, it should, as far as possible, be integrated into the existing health services. Training local health-service staff in how to administer or monitor an intervention is generally preferable to employing or importing new study staff who will leave once the project is over, for example. The use of a pragmatic study design—based on simple, locally relevant procedures, flexible protocols, and minimal data collection—will not only make the study more feasible to conduct; it will mean that the intervention, if proven to be effective, should have fewer barriers to implementation.

Despite the difficulties, there is evidence of progress. Although few randomized trials are conducted in developing countries, the numbers have increased. For example, the number of trials in sub-Saharan Africa rose almost threefold between 1980 and 1999. However, not all of these studies addressed conditions related to the global burden of disease, or the health needs of the local population. Conditions arising during the perinatal period fared particularly poorly. In another survey of trials related to HIV/AIDS in Africa, 15 studies were identified, all from sub-Saharan Africa, which evaluated interventions to prevent mother-to-child transmission (Nandi Siegfried, personal communication). The earliest was published in 1998. Four of these studies were single-centre, six were multicentre within one country, and five were multicentre and multinational. Of these five, one included centres in Europe as well as Africa, whilst the remaining four used only African centres. Overall, 10,448 participants were recruited to these studies, the smallest of which had 75 participants and the largest 1797.

One story—that of calcium supplementation for prevention of pre-eclampsia—demonstrates the potential for perinatal research in developing countries. The suggestion that dietary calcium might explain at least some of the variation in incidence of pre-eclampsia was first put forward in 1962, based on tentative observations of the similarities and differences between pregnant women in Australia and in Ethiopia. An inverse relationship between calcium intake and hypertensive disorders of pregnancy amongst Mayan Indians in Guatemala was described in 1980, when it was proposed that this association might be causal. Initial trials to test this hypothesis were conducted largely in South America and India. Taken together, these studies suggested calcium supplementation reduces the risk of pre-eclampsia by about one-third, but the data were insufficient for firm conclusions about the possible effects on more substantive outcomes such as perinatal death and preterm birth. The recently completed international study recruited 8325 women with a low calcium intake in six developing countries. Results are expected soon.

A subset of the children born to women recruited from private clinics into one trial in Argentina have been traced for 7 years, and 13-year follow-up is under way (Edgardo Abalos, personal communication). Long-term follow-up of children recruited to perinatal trials remains one of the great challenges, although clearly it is possible in at least some middle-income countries.

Asking the right question

Research is about asking questions and then finding and testing answers. If the question is wrong, or unclear, the answer is unlikely to be helpful. To decide whether an intervention does more good than harm, formulating the
question involves deciding who are the people who have the problem, what are the interventions to be compared, and what outcomes need to be measured. In rich countries most pregnant women are healthy and well-nourished. The same is not true in poor countries. So, for example, there is now strong evidence that routine iron supplementation during pregnancy is not worthwhile in Western countries. As all the trials in this systematic review were conducted in developed countries, however, this result cannot easily be applied to the many developing countries in which chronic anaemia is endemic.

HIV/AIDS is a global problem. Although strong and persistent advocacy has given it a high profile in developed countries, over 98% of the global burden of disease is in middle-income and low-income countries. One of the major public health concerns in countries with a high prevalence of the HIV virus is prevention of perinatal transmission. In developed countries a series of trials in the mid-1990s demonstrated that taking antiretroviral drugs during pregnancy and delivery dramatically reduced the risk that infants born to HIV-positive women would have the virus. The problem for developing countries was that these drug protocols were unaffordable. One solution appeared to be using a much shorter, and therefore more affordable, course of an antiretroviral drug, but whilst these trials were still ongoing controversy erupted. Whether it is ethical to use a placebo for the control group in a developing country when known effective drugs exist, even though those drugs are not affordable or available, was hotly debated. This issue remains controversial, although some regard it as acceptable to offer the control group the highest standard of care attainable in the country where the study is being conducted.

In many poor countries postpartum haemorrhage remains an important cause of maternal mortality and morbidity. Injectable uterotonic in the third stage of labour offer the best protection against postpartum haemorrhage. However, these are not available in many rural areas of the developed world where women deliver at home, without access to either refrigeration to store the drug safely or to anyone with the training to give injections. In these settings, an oral agent which is stable over a range of temperatures, such as misoprostol, offers considerable potential advantages. If misoprostol does have some protective effect against postpartum haemorrhage, without any unforeseen adverse effects, this could potentially be beneficial. So, whilst a trial comparing oral misoprostol with placebo might not be ethical where active management of the third stage is the norm, it may be relevant for some settings in developing countries.

A rather different example is the evaluation of routine antenatal care. Antenatal care first evolved around 1910 as a response to concern about persistently high levels of maternal mortality in Western countries. A package of antenatal care was outlined in a Ministry of Health document published in the UK in 1929. This document specified the minimum scope and intervals for antenatal care, with a first visit at around 16 weeks followed by 4-weekly visits to 28 weeks, fortnightly to 36 weeks, and weekly thereafter with each visit including abdominal palpation, fetal heart auscultation, urine testing and general health enquiries. No explicit rationale was offered for either the spacing or clinical content of visits. Nevertheless, these guidelines were to establish the basic pattern for antenatal care into the next century.

Only after more than 50 years was there sufficient doubt about the benefits conferred by antenatal care to prompt rigorous evaluation. There have now been several randomized trials evaluating the timing, content, and care-giver for antenatal care. Trials conducted in developing countries have all compared the current standard package of care with a reduced number of visits. By far the largest of these was conducted in 53 hospitals in Argentina, Cuba, Saudi Arabia and Thailand. This large multicentre trial used cluster, rather than individual, randomization. It concluded that the new package of four goal-oriented visits was as good as the traditional multiple visits. The conclusions of a systematic review of all relevant trials were that although providers of antenatal care are unlikely to realize actual cost-savings from a lower number of antenatal visits, women’s time and energy, along with staff and buildings, would be freer for other more useful activities.

Innovation and hypothesis generation

Public-sector health professionals working in developing countries are often subjected to enormous clinical workloads. While this is not an ideal situation, it does expose individuals to an exceptionally broad clinical experience, which may lead to identification of disease patterns or the generation of novel therapeutic ideas. One example of this is the independent observation of apparently low rates of pre-eclampsia in Ethiopia and Guatemala, and the suggestion that this might be related to calcium-rich diets in these populations. Another is the development of the partogram for monitoring labour progress in midwife-run obstetric units linked to a busy referral unit in Harare, Zimbabwe. Lack of resources may also provide the stimulus for health workers in poor countries to seek new, affordable interventions for common problems. An example is the off-label use of misoprostol for a number of obstetric indications. Health workers from developing countries have been responsible for several innovations, such as the use of misoprostol for labour induction at term, and use of a misoprostol solution to titrate small doses for labour induction. The first randomized trials of misoprostol for the prevention and treatment of postpartum haemorrhage and use of the rectal and sublingual routes of administration were from developing countries.

Protecting participants in research

The ethical issues raised by research collaboration, both within poor countries and between rich and poor countries, are many and complex. Firstly, there is the danger that vulnerable people in poor countries, such as women and children, may be exploited for research which would be difficult to carry out in affluent countries. A series of international agreements on strategies to protect participants in research, dating back to the Nuremberg principles of 1947, have provided guidelines for researchers, but adherence to these principles does not necessarily eliminate the
possibility of exploitation. Conversely, there may occasionally be situations in which a local ethics review committee might approve a deviation from this standard in order to address an important health problem in that particular country. 37

One particularly difficult issue is that of attempting to avoid any activity which may be seen as an inappropriate inducement to women, or their families, to participate in research. For women with very limited access to healthcare, participation in a research trial will often mean greatly improved access to health-care in general, and sometimes access to specific treatment (such as surfactant for premature babies) which otherwise would not be available to them. It is almost impossible to avoid some of these realities acting as an inducement. On the other hand, it can be argued that to withhold research from poor communities on the grounds that the access to improved care for participants will act as an inducement would be to deprive them of specific care that would ordinarily not be available to them. However, if such additional care is offered, there should at least be some agreement with the local community about when such provision will be withdrawn once the study ends. This is particularly important for long-term care, for example antiretroviral drugs for women or children who are HIV-positive.

**Implementation and changing practice**

Effective implementation of evidence-based practice remains a significant challenge. 38 Having access to information alone is unlikely, by itself, to lead to significant improvements in health-care. 38 Active information dissemination and implementation strategies are more likely to achieve change, although the evidence base to support this is not strong. 39

The WHO Reproductive Health Library (RHL) is an annually updated electronic publication distributed free of charge in developing countries. It includes predominantly Cochrane systematic reviews in reproductive health, together with commentaries written by experts who are familiar with under-resourced settings, short practical guidance documents, and implementation aids (such as educational videos) to facilitate the adoption of evidence-based practices. To try to assess the impact of the RHL, a multicentre cluster randomized trial was conducted in 40 hospitals in Mexico and Thailand. 40 The intervention consisted of three interactive workshops using RHL over a period of 6 months. The focus of the workshops was to provide access to knowledge and enable its use. The main outcome measures were changes in clinical practices, as recommended in RHL, a year after the first workshop. 41 The multifaceted, active strategy to provide health workers with the knowledge and skills to use RHL to improve their practice did lead to increased access to, and use of, RHL. However, no consistent or substantive changes in clinical practice were detected. 42 Access to knowledge is essential but probably not sufficient in itself to lead to change in health-care practices in the short term.

**Collaboration and research networks**

The perinatal field has many good examples of locally initiated and conducted research, of international trials coordinated within a developing country, and of international trials coordinated from a developed country.

Collaborative networks linking researchers and clinicians in developed and developing countries have the capacity to tackle important issues for maternal and perinatal health in developing countries. Many of these studies also have relevance for the developed world. One example of such a network is that coordinated by the Department of Reproductive Health and Research at WHO. This network has successfully conducted a number of important multi-centre randomized trials involving centres in Argentina, China, Cuba, Egypt, India, Mexico, the Philippines, Saudi Arabia, South Africa, Thailand and Viet Nam. These trials have addressed topics as varied as evaluation of a new antenatal care model, 26 misoprostol for the third stage of labour, 43 a programme promoting evidence-based medicine based on the WHO Reproductive Health Library, 40 and calcium supplementation to prevent pre-eclampsia. 15 Ongoing studies coordinated by this network include trials evaluating the effectiveness of alternative nitrofurantoin regimens for asymptomatic bacteriuria during pregnancy, sublingual misoprostol for postpartum haemorrhage, and vitamins E and C for prevention of pre-eclampsia. 44

Another network has focused on prevention and treatment of eclampsia, and has conducted two major international randomized trials. 45, 46 The first 46 was designed to show which of the ways being used to treat women with eclampsia (seizures superimposed on pre-eclampsia) worked best. The background was that an estimated 50,000 women die each year having had an eclamptic convulsion. 47 Although case fatality is high throughout the world, 99% of these deaths involve women in developing countries. For decades, debate had raged about which anticonvulsant was preferable for treatment of eclampsia. Whilst this debate continued, women continued to suffer and die in large numbers, having received interventions introduced on the basis of personal opinion and poorly controlled studies. This study recruited 1687 women at 27 centres in nine developing countries. 46 Magnesium sulphate was clearly more effective than either phenytoin or diazepam. 46 It has been described as the ‘most important trial of the twentieth century’, 48 and when published the journal editor commented: ‘what a triumph for the trialists but a scandal that we had to wait 70 years for the answer’. As noted in the trial report, 46 from magnesium sulphate first being suggested for eclampsia (in 1906) to the introduction of diazepam and phenytoin (in 1968 and 1987, respectively) a possible 42 million women would have had an eclamptic convulsion, and 4 million of them may have died. Unexpected outcomes of this study were that it challenged assumptions about the pathophysiology of eclampsia, 49 and that it changed practice rapidly in developed countries where magnesium was not being used. 50, 51

The next question was whether magnesium sulphate also prevented eclampsia when given to women with severe pre-eclampsia. Again, there was little reliable evidence. The balance of benefit and harm for seizure prophylaxis is quite different from treatment. Most women and their babies do well following pre-eclampsia, and we are not good at predicting who will develop eclampsia. Even if magnesium sulphate reduced the risk of eclampsia, it needed to be very safe to be worthwhile. Although most
maternal deaths are in the developing world, many women in developed countries become severely ill during pregnancy from conditions like pre-eclampsia. Hence this question is directly relevant to developed as well as developing countries. In the second study, 10,141 women participated in a randomized comparison of magnesium sulphate with placebo at 175 centres in 33 countries across four continents; 85% of recruitment was from developing countries. Magnesium sulphate more than halved the risk of eclampsia among women with severe pre-eclampsia, without substantial adverse effects. Centres in 19 countries helped to assess long-term outcome for the children and their mothers. The philosophy that any information about a child is better than none enabled successful tracing of children in settings where follow-up had previously been dismissed as impossible, demonstrating how dedicated and collaborative commitment can achieve high follow-up rates even in the most unpromising circumstances. Magnesium sulphate is relatively cheap to produce. This research provided strong evidence to support it being made available for prevention and treatment of eclampsia throughout the world.

Facilitating collaboration

Successful collaboration to tackle complex health problems will usually involve working jointly with a range of people from different backgrounds and disciplines. Stimulating and harnessing the collective effort can be both productive and rewarding. The concept of collective ownership is not only that the study is owned by everyone who contributes to it, but also that there is benefit for all. For example, the fact that the Collaborative Eclampsia Trial was launched in Spanish before English probably helped to set the tone for the collaboration that emerged subsequently. Our experience is that important factors in fostering truly collective ownership are: early and widespread consultation on development of the study protocol and trial materials; early and explicit agreement about sharing results with collaborators before submission for publication, authorship and dissemination; face-to-face contact between collaborators, as well as between those responsible for coordination and collaborators; flexibility; being inclusive of everyone contributing, not just senior staff; rapid acknowledgment of all communication from collaborators; and regular and frequent feedback to each centre on their progress and that of the study overall.

Feedback from collaborators in developing countries is that benefits they particularly value include the sharing of knowledge and expertise; enhancing their own capacity to do and to utilize research; appropriate acknowledgement of all contributions; and opportunities to overcome political, cultural and economic barriers to networking and friendship. Another benefit, often difficult to measure, is generating enthusiasm for research particularly in clinical settings, which may be lacking in developing countries. Belonging to an international collaborative group may help motivate people to do their own local research.

Authorship for collaborative research is often published as a collaborative group. Even though each paper lists large numbers of contributors, there remain even more people whose names do not appear but who have, nevertheless, made substantive contributions. For example, junior doctors, midwives and nurses who helped with recruitment and follow-up, and secretarial or administrative staff who facilitated efficient running of the study locally. One strategy to overcome this problem is to give everyone certificates of collaboration. Those with certificates can then add the study to their curriculum vitae, even if they are not listed on the publication.

Conclusions

The need for high-quality, relevant perinatal research in developing countries is compelling. There are many examples of good perinatal research in developing countries. Nevertheless, significant challenges remain, and these are being tackled. We need better information about maternal and perinatal health, and about performance of the health services; we need more evaluation of what helps and harms within the existing health services; and we need improved strategies for implementation of research findings.

Practice points

- Research is a vital tool for identifying and tackling health problems.
- Reliable data on morbidity and mortality are scarce in many developing countries.
- This lack of up-to-date reliable information makes planning and evaluation of maternal and neonatal health-care difficult.
- Access to knowledge is essential, but probably not sufficient in itself to lead to improve health-care.

Research directions

- Of the funds for health research worldwide, 10% is directed towards diseases which contribute 90% of the global burden of disease. Reducing barriers to research in the developing world is crucial if this balance is to be redressed.
- The need for perinatal research in developing countries is compelling. Such research is possible; much has already been achieved, but more is still needed.
- As far as possible, trials should be integrated into the existing health services.
- Researchers need to ask the right questions for developing countries.
- Collaborative networks have the capacity to tackle important issues for maternal and perinatal health in developing countries.
References


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*The important references are indicated with asterisks.*