XXXIV ACHR

Meeting of the Advisory Committee on Health Research of the Panamerican Health Organization 12-14 July 1999

RESEARCH ACTIVITIES OF THE LATIN AMERICAN CENTER OF PERINATOLOGY

Research Coordination
Division of Health and Human Development
Pan American Health Organization
Pan American Sanitary Bureau • Regional Office of the World Health Organization
Washington, D.C.
1999
Executive Summary

Analysis of perinatal and maternal mortality in Latin America and the Caribbean shows that there has been little improvement in the past 25 years and reveals alarming disparities with the more developed nations. The international scientific community, headed by the developed nations, makes few contributions to solving the priority problems of our countries.

In addition, in health care, practices with proven benefits must be employed, and those without benefits or that can even cause harm must be discarded. However, many inefficient practices continue to be employed, while others of proven benefit have not been adopted.

Given the above, CLAP research strategies aim to:
1. Determine the priorities associated with poor outcomes in pregnancy and childbirth in the Region;
2. Determine which practices should be employed and which should be discarded;
3. Identify appropriate practices geared toward on our priorities, through research; and
4. Improve the implementation of appropriate medical practices and discard inappropriate ones.

In order to achieve these objectives, CLAP collects and analyzes regional databases and conducts critical analysis of scientific literature, performs collaborative clinical research, investigates methodologies for incorporating evidence-based medicine, and provides education and mass dissemination of evidence-based medicine.

This document presents the research activities under way and programmed by CLAP, which, together with education and technical cooperation, are the three pillars of the Center's activity.
1. Introduction and Rationale

Maternal and perinatal health are a huge problem for less developed countries.

An examination of mortality trends in our Region reveals that infant mortality has declined in the past 25 years, while perinatal mortality has changed little. Statistical analysis of a select group of countries with good estimators of infant and perinatal mortality in the Region shows that between 1970-1974 these countries had an infant mortality rate of 56.2 per 1,000 and a perinatal mortality rate of 30 per 1,000. In 1995 infant mortality in those countries had fallen to 17.1 per 1,000, while perinatal mortality had only dropped to 24 per 1,000. Throughout the Region infant mortality in 1995 was 31.5 per 1,000 and perinatal mortality 39.4 per 1,000. In other words, perinatal mortality is currently higher in our Region than infant mortality.

The two most developed countries in the Americas (Canada and the United States) have perinatal mortality figures of 10 per 1,000, compared to 19.9 per 1,000 in 1970. The significant drop in those countries is attributed chiefly to the use of sophisticated technologies in neonatal care. As a result, it can be observed that the reduction in perinatal mortality in our Region has been small, that the disparities with the developed countries are growing, that perinatal mortality is higher than infant mortality, and that the solutions employed by the developed countries cannot be applied to our own. Furthermore, the analysis of infant mortality reveals that the perinatal component is the leading cause of death in children in the Region, accounting for over 50% of these deaths.

In addition, 14% of the children born in our Region have low birthweight, compared to 6.9% in the developed countries. Low-birthweight infants in our Region predominantly exhibit harmonious growth retardation, i.e. they experience
a chronic alteration in fetal growth. These infants exhibit poorer subsequent development.

The monitoring of infants with low birthweight has shown that those children are five times more likely than infants born with adequate weight to die in the first year of life, twice as likely to be hospitalized for diarrhea and pneumonia in the first two years of life, 3.5 times more likely to have high blood pressure at age 15, 1.6 times more likely to have a low intelligence quotient, 5 times more likely to be of short stature, and, when they become mothers, 2.2 times more likely to have a low-birthweight baby. All this documents the tremendous problems linked with insufficient intrauterine growth. Global research has paid little attention to this problem, since it is not a priority in developed countries. Out of 8,361 random clinical trials conducted in perinatology, only 103 (1.3%) considered fetal growth as the principal variable of the outcome. This means that there are no interventions whose effectiveness has been evaluated through valid scientific research, making it possible to promote or advise against them as strategies for improving fetal growth.

Maternal mortality figures continue to be alarming and have failed to improve in the past 25 years. Although 80% of maternal deaths can be attributed to abortions, hypertension, hemorrhage, obstructed labor, and infections, it has not yet been possible to improve the indicators. Solutions have not yet been found for many of these complications. The etiology of hypertension in pregnancy is unknown, and most of the preventive measures studied have not yielded conclusive results. Prevention of postpartum hemorrhage requires intravenous and heat-degradable drugs, which sometimes hinders implementation under field conditions. It is very difficult to detect obstructed labor in a timely fashion in order to effectuate change. Furthermore, there still is little information in our countries on factors related to prevalent pathologies, which hinders their prediction and prevention.
In addition, the prevalence and consequences of a series of problems in our populations, such as domestic violence, habits and vices, and the nutritional cost of pregnancy and breast-feeding in adolescents, is unknown. This has made it difficult to determine the priority that these problems should be given in health care.

As indicated by the situation outlined in this introduction, it is clear that the priorities in our countries differ from those of the developed countries. However, it is the developed countries that for the most part set the priorities and influence the allocation of most of the world’s resources.

Also, as noted above, investigators do not concentrate their efforts on a search for solutions to our priority problems, and we therefore do not have a proven set of interventions to apply. Moreover, we have observed that many behaviors proven efficient in perinatology and maternal care are not used in our Region, while ineffective and even harmful ones continue to be employed.

As a result, we can conclude that the countries need to have a clear knowledge of their priorities. If not, they will tend to adopt the priorities of the developed countries, which have been widely accepted. On many occasions, the considerable influence of these countries has led to the use of costly technologies for the care of our population, many of which have not been well tested. It has been seen, for example, that the costly prenatal monitoring that is widely practiced in our Region does not improve perinatal outcomes and even increases cesarean deliveries. We should require rigorous testing of any new treatment or preventive or diagnostic method before including it in medical practice and, thereby, reduce the human and economic costs.

In addition, we must ensure that our health care teams are able to conduct critical reviews of the medical literature and that guidelines or standards emerge
from this practice that can be applied in our care. It has been seen that, when developing standards, the most prominent physicians of a country are cited, who impose the experience gained in their practice. Proper regulations should be drawn up based on a critical review of the literature and an analysis of the country data; this will make it possible to set priorities and to select interventions and procedures with proven benefits.

In light of the above, CLAP has established a research plan aimed at:

- determining the perinatal and maternal health priorities of the Region and the principal factors that influence them;
- determining which interventions are proven in order to recommend and employ them in maternal and perinatal care;
- generating changes in health care providers and users for detecting beneficial practices and applying them; and
- conducting research aimed at providing solutions to the priority problems.

2. Clap In Maternal and Perinatal Health Research

Over its nearly 30-year history, CLAP has been identified in the Region as a leader in perinatal and maternal research. This facilitates the introduction of its teaching methods and the conducting of research.

During this period, CLAP has set up a unique data collection system in many centers of the Region, producing a database with numerous data that is representative of the Region. Through analysis of the database, priorities can be established and the factors related to maternal and perinatal outcomes detected.
This relationship with the countries has led to collaborative research, many training courses, and presentations at meetings and congresses, all of which has resulted in a new initiative—the formation of a network of CLAP collaborating centers in the Region. This initiative was recently launched and, since it was first announced, we have received proposals for collaborating centers from virtually all the countries in the Region. Given the meticulousness necessary for this initiative, to date one center in the Dominican Republic and another in Mexico have been incorporated in the network, and the immediate incorporation of a center in Chile, Colombia, Brazil, Ecuador, and Argentina is pending. These centers will teach, collect and analyze data, implement best practice, conduct both their own and collaborative research, and disseminate the best care. This initiative has united the efforts of the WHO Special Programme of Research, Development, and Research Training in Human Reproduction and its collaborating centers.

CLAP’s central structure includes a corps of professionals with training in clinical research and evidence-based medicine. Weekly seminars are held on methodological topics, conducted either by these professionals or guest experts. CLAP has a well-stocked documentation center and systems for conducting literature searches. It has a team of computer specialists proficient in a variety of software, who stay on top of developments in their field. The support staff functions much like research assistants, collaborating with professionals to coordinate different the different research projects.

3. Purposes And Strategies
The purpose of CLAP is to contribute to a reduction in maternal and perinatal morbidity and mortality in the Region by implementing evidence-based practices, prioritizing the principal problems.

In order to achieve these purposes, CLAP employs the following strategies:

1. Analysis of regional priorities and the factors that determine them;
2. Definition of effective practices;
3. Research aimed at finding solutions to the priority problems; and
4. Improving the quality of care by employing effective practices.

4. Work Program

4.1. Analysis of Regional Priorities and the Factors that Determine Them

Rationale

As stated above, knowledge about our situation and focusing health actions and research on the priorities are essential. Furthermore, it is necessary to determine what conditions or factors are most closely related to poor outcomes in our populations in order to target actions toward those groups, rather than diversifying efforts in very low-risk groups, which would achieve few results. This principle also guides CLAP programming, concentrating efforts and orienting the support requested and received.

Activities

4.1.1. Development and Analysis of Existing Databases
PAHO makes a great effort to obtain and document vital statistics from the countries of the Region, which can be accessed through the PAHO Intranet. Several international agencies and countries also make similar efforts. CLAP is preparing databases with this information, producing periodic analyses that characterize the perinatal and maternal situation in the Region and differences between countries. These analyses are tabulated, discussed at periodic CLAP meetings, disseminated by diverse means, and interpreted. These interpretations give rise to the identification of priority problems, a regional consensus on the principal problems, and recommendations. A system for periodic updating is being developed that will be easy to analyze and interpret and that can be accessed on the Internet by users in the countries of the Region.

4.1.2 Database Development and Analysis

Activities in Progress

CLAP has developed a database from the registry of pregnancies in the Region, containing a total of 1.2 million births in 20 countries in Latin America and the Caribbean from 1985 to the present. For each pregnancy there are 170 variables. This database is permitting a long series of analyses that will make it possible to determine the perinatal and maternal situation in the Region and quantify the factors that influence outcomes. The list of publications includes a series of analyses already conducted or currently under way, such as:

- Factors associated with hypertension in pregnancy
- Maternal age and maternal-perinatal outcomes
- Intergenesic interval and its link with maternal-perinatal outcomes
- Maternal nutrition and maternal-perinatal outcomes
- Multiple pregnancy and maternal-perinatal outcomes
Activities to be Conducted

There are almost 2 million registries in the countries that have not been incorporated into this database. Negotiations are under way to have the countries send the registries to expand the database and make it more representative of the Region. It is hoped that at least 1 million more registries will be incorporated by the end of the year 2000.

At least three more analyses of this database are scheduled in the next two years:
- Adolescent pregnancy: its risks and the factors associated with outcomes;
- Principal factors associated with maternal and perinatal outcomes and analysis of their risk; and
- Evolution of processes and outcomes in Uruguay.

4.1.3. Development of Computer Applications for Research, Epidemiological Surveillance, and Improving the Quality of Perinatal Care in Health Services

The Perinatal Information System (SIP), developed by CLAP in 1983, consists of a set of clinical registries, with software for data entry, statistical analysis, and the generation of reports. The SIP 2000 will be part of the epidemiological research tool with the widest global dissemination in the public domain: Epi Info. These upcoming versions will be for Windows 95, 98, and NT, further facilitating their use by health professionals. This joint effort between PAHO and the U.S. Centers for Disease Control and Prevention will also facilitate the production of training materials on clinical and epidemiological research in the countries; distance-learning resources will also be used.
The influence of SIP as the standard in developing perinatal health indicators in the local health services can be gauged by the more than 3,000 software diskettes that have been distributed and its status as the official registry for many of the countries in the Region that have adopted it. The heightened influence anticipated with this new version of the SIP, together with Epi Info, can be seen in the distribution figures for this epidemiological statistical program, estimated at 150,000 copies.

This initiative will further promote research capacity in the Region and the training of additional human resources.

4.2. Definition of Effective Practices

Rationale

One method for achieving efficient, effective health care is determining which practices have proven benefits and which should be discarded because they have proven inefficient or even harmful. A center such as CLAP should keep the information on practices very up to date, since it is considered the Region's clearinghouse in this area.

Activities

4.2.1. Systematic Reviews

Through systematic updates, CLAP has analyzed the practices most frequently employed in its specialty. To this end, it conducts critical analyses of changes in practice found in the literature and determines the usefulness of these practices. It is also making changes that will be incorporated in the Cochrane Database and the Reproductive Health Library.
4.2.2. **Dissemination of Practices**

Through the media that CLAP has at its disposal, there is intensive effort to disseminate information on which practices to employ and which to discard. The CLAP Bulletin has a circulation of 8,000 and is sent to ministries, medical, nursing, and midwifery schools, health professionals, health centers, etc. The Bulletin promotes practices in a simple manner, with due justification. CLAP participation in congresses and courses also helps to disseminate these practices, together with the rationale behind their use or rejection.

4.2.3. **Participation and Dissemination of Critical Reviews**

CLAP collaborates with the Cochrane Database, which has revised the protocol for episiotomies, which is updated periodically. The revised protocol for the kangaroo care method, which will be included in the next update, has just been accepted. In addition, CLAP collaborates with the WHO Reproductive Health Library. It has participated in several updates, which it delivers and disseminates in the countries and translates into Spanish.

4.3. **Research for the Solution of Priority Problems**

**Rationale**

The systematic updates mentioned above do not offer solutions to all the problems, and the majority of research in perinatology has been conducted by investigators from developed countries with priorities that are different from ours. Thus, research must be conducted to find solutions that will address the priority problems in our Region and improve the situation. CLAP has detected a serious and growing problem in our Region: the high rate of cesarean sections in some countries. These countries have the highest rates in the world, which is
paradoxical, since cesarean sections are more common among higher-income women. A review of the literature shows that there is little research on interventions to reduce the number of cesarean sections. CLAP therefore believes that it should contribute interventions to reduce the use of this procedure without causing harm.

The introduction mentioned the significant problem of retarded fetal growth and the few proven contributions that can improve growth. This will be CLAP's priority research area over the next three years. CLAP will therefore conduct a series of research activities aimed at better understanding the mechanisms involved in fetal growth and the factors that influence it and will explore interventions to improve fetal growth.

Randomized Study on Second Opinions in Decisions to Perform Caesarean Sections

- Research in Progress

This is a randomized study using the cluster method in which participating hospitals will be instructed at random to seek a second opinion in deciding whether to perform a cesarean section or continue with customary practice. Prior to commencing the study, for six months the hospitals will collect information for the database on the incidence and causes of cesarean sections and vital statistics. Following this period, the hospitals will be randomly paired, based on geographic location and the percentage of cesarean sections. A total of 36 hospitals are required in order to detect a 25% difference in the incidence of cesarean sections, with a power of 80% and a 5% margin of error. A total of 42 hospitals were recruited from 6 countries in the Region, as follows: 18 in Argentina, 8 in Brazil, 6 in Colombia, 4 in Cuba, 2 in Guatemala, and 4 in Mexico. Cuba began the intervention in May 1999, and the other countries will follow in June and July 1999. The intervention stage will last six months. It consists in
requesting a second opinion when deciding to perform a cesarean section. The physician consulted should personally treat the patient at the hospital and, with the attending physician, make a series of decisions based on the evidence available. This study is being financed by the European Commission, and European researchers sit on its steering committee.

Interventions to Improve Fetal Growth

This will be CLAP's main area of research and will be approached from several angles.

- Research in Progress

Epidemiological Studies. The existing databases at CLAP will be utilized, including: (1) the database of the perinatal information system, which is comprised of 1,200,000 pregnancies in 20 countries of the Region, with 170 variables in each registry; and (2) the database on the cohorts in Pelotas. There are two cohorts from whom information was gathered on all births in a one-year period in Pelotas, Brazil. These children were followed, and notes were taken on their vital information, morbidity, and physical and intellectual development. The first cohort was born in 1982 and the second in 1993. Using these databases, studies will be conducted on the association between factors from preconception and conception and fetal growth and the subsequent evolution of the infants. The goal is to identify the main variables that influence fetal growth and determine how they influence survival and the subsequent development of the children. This will make it possible to gear interventions toward the factors more closely associated with and that have the greatest impact on development.

- Research in Preparation
**Intervention Studies.** Random clinical trials will be planned to test various interventions that could improve fetal growth. They will be selected from several sources. First, there is a review of the content of the literature on promising interventions in fetal growth mechanisms. Secondly, there will be information from the analysis of the databases on the factors with the highest attributable risk and the greatest long-term consequences. Finally, there will be a review of basic studies on fetal growth mechanisms and the factors involved.

These reviews will be completed in 1999, and CLAP expects to have proposals to begin random clinical trials on several interventions in 2000. Some of this promising research includes:

- **Folate supplementation for pregnant adolescents.** This will be a random clinical trial in which pregnant women under the age of 20 will be instructed at random to receive a 400-mcg supplement of folic acid or a placebo; 1,800 pregnant women will be needed in each group. A 33% drop in the prevalence of intrauterine growth retardation in the pregnant women receiving supplements is expected.

- Other possible interventions are: *nutrient supplementation with l-arginine, magnesium, and zinc.*

**Monitoring Infants in Uruguay with a Birthweight of under 1500 g**

- **Research in Progress**

Objectives:
To conduct an epidemiological study on morbidity and mortality in infants with a birthweight of under 1500 g in greater detail than the study permitting the collection of vital statistics for birth and death certificates and the information currently being collected in the institutional area.

To provide participating institutions with data that could be useful for managing the quality of the services, continuous improvement, and internal auditing.

Population:

- All live births under 1500 g in Montevideo between 1 May 1999 and 30 November 1999. There will be an estimated 20,000 to 22,000 births, and approximately 250 infants with a birthweight of under 1500 g. The neonates will be followed until they are discharged from the hospital.

This study is being conducted with the collaboration of the Neonatology Committee of the School of Nursing of Uruguay.

After this experiment, the implementation of this same model in other situations in Latin America and the Caribbean will be proposed, launching a collaborative network that will make it possible to disseminate the results of the care for this group of infants and facilitating the improvement of quality.

Interventions to Improve Maternal Health

Random Clinical Trial on Calcium Supplementation during Pregnancy for Women with low Calcium Intake to Prevent Preeclampsia

- Research in Preparation (to begin possibly in January 2000)
Studies to date have shown that for women with low calcium intake, calcium supplementation is a promising intervention for reducing the onset of preeclampsia. This pathology is prevalent in less developed countries and is among the leading causes of maternal death. Intake studies show that the average calcium consumption is 350 mg per day in developing countries, which is much lower than the recommended level for pregnant woman (1,100 mg/day).

As a result, it is important to conduct research on pregnant women with low calcium intake. This study will be a collaborative effort coordinated by CLAP jointly with the WHO Special Programme in Research, Development, and Research Training in Human Reproduction and the Dunn Clinical Nutrition Centre at Cambridge University in the United Kingdom. The original protocol has been drafted, and centers in different continents have been contacted to participate. The Centro Rosarino de Estudios Perinatales in Argentina may participate, as well as others in Africa, India, and Asia.

Nutritional Cost of Pregnancy and Breast-feeding in Adolescents

• Research in Progress

It is alarming to see that throughout the Region adolescent pregnancy is very frequent (between 14 and 25% of all pregnancies, depending on the country). The fact that these women are adolescents places an increased nutritional burden on them, given the demands of pregnancy and breast-feeding and adolescent growth. Little is known about the effects of pregnancy and breast-feeding on the nutritional status of adolescents. Learning about this would be valuable, since once they finish breast-feeding, these women must meet their own and their child’s nutritional requirements, which impacts on their quality of life and the care they provide for their child. A study will be conducted on 1,000
adolescent women from low-income populations in countries in the Region in which nutritional status will be studied six months postpartum and will be related to various variables of pregnancy and breast-feeding. The purpose is to evaluate the nutritional cost and provide nutritional recommendations for pregnant and breast-feeding adolescents.

Research on Adolescents in the 1982 Birth Cohort in Pelotas, Brazil

Research in Preparation

Through its collaborative work with the Universidade Federal de Pelotas, Brazil, CLAP is participating in the preparation of the research protocol on adolescents in the 1982 birth cohort.

In the year 2000, when the children in the cohort turn 18, all males, by law, must register for the draft in their city of birth. This represents is a unique opportunity to interview them, take down their physical variables, and collect specimens for laboratory analysis. Contact has been made with the Brazilian army, and the possibility of conducting the work throughout the year in 2000 has been guaranteed.

The main purpose of the project is to analyze the Barker hypothesis on intrauterine determination of chronic degenerative adult diseases. To our knowledge, this is the only large cohort followed from birth through adolescence in a developing country.

Discounting all deaths, 2,652 males are expected--1,713 born at term with appropriate weight; 313 small for their gestational age (Williams P<10); and 102 preterm. Furthermore, there were 524 males who at birth had an unknown gestational age, but for whom birthweight information exists.
4.4. Improving the Quality of Care through Effective Practices

Rationale

One mechanism for improving the quality of care is knowledge of the principal problems and outcomes. In addition, use of best practice is essential for high-quality care. A major challenge at present is not only obtaining knowledge about best practice but ensuring that health professionals stop using practices that have no benefits or are harmful and incorporate new practices proven to be efficient.

Activities

4.4.1. Interpreting the Data Collected

Two such activities are under way. First, the SIP will be incorporated into Epi-Info 2000, and CLAP is preparing user-friendly output enabling the health services to see the progress of the service. The output will show the composition of the population, the principal risk factors, and the outcomes obtained. Simple tables and figures will permit interpretation of the outcomes, their evolution over time, and the detection of warning signs that should lead to action.

A course scheduled to begin in the year 2000 is being developed to provide training on the interpretation of health service vital statistics.

4.4.2 Training in Evidence-based Medicine

How to Change Practices
One condition for change in health care is that health professionals understand evidence-based medicine. CLAP has developed and offers courses on evidence-based medicine at its headquarters and in the countries. These courses have different formats and levels of complexity. One is a classical course developed by McMaster University in Canada on the resolution of clinical cases. Another is on preparing standards and guidelines for evidence-based perinatal care. Students are trained to maintain these standards in their work. Another course provides training on conducting critical reviews. They are being taught in the region, and attempts will be made to expand their dissemination and scope through the training of multipliers.

These courses were conceived as a strategy; however, they will be evaluated to assess their efficiency.

In this context, during 2000-2001, protocols will be developed aimed at evaluating strategies to facilitate the incorporation of and changes to the practices of health care providers.

4.4.3 Social Studies on Acceptance of Medical Practices

CLAP plans to conduct social studies among health service users and providers. For users, it will investigate how practices are employed and accepted. For providers, it will look at the mechanisms that lead them to employ or change practices. These studies are scheduled to begin in the year 2000. The research that CLAP conducts on new practices includes an evaluation of user and provider satisfaction in order to facilitate subsequent implementation of the practice.

A protocol has been developed to investigate how user knowledge influences the incorporation of practices. From the populations selected, some will be randomly chosen to participate in the mass dissemination of best practice for health care during delivery and then compared with populations that do not receive that
information. In all the communities (control and experimental) health care providers will be trained in these practices.
5. CLAP Publications (July 1997-May 1999)


PAPERS IN PRESS (ACCEPTED FOR PUBLICATION)


3. Barros FC, Victora CG. Increased blood pressure in adolescents who were small for gestational age at birth: a cohort study in Brazil. Int J Epidemiol.


PAPERS SENT FOR PUBLICATION


7. Simini F. The perinatal information system SIP: a clinical database in Latin America and the Caribbean.

PAPERS IN PREPARATION


