Global Alignment, Coordination and Collaboration in Perinatal Research: The Global Obstetrics Network (GONet) Initiative

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Medical interventions should only be offered if there is evidence that they help the patient. At present, there is consensus that the effectiveness of medical interventions should be evaluated before they are incorporated into guidelines. The randomized clinical trial (RCT) is considered to be the best research tool to evaluate the effectiveness of medical interventions and is widely acknowledged as the design of choice for evaluating medical and surgical treatments. 1-3

Good clinical studies start with a relevant question and solid design. However, they can only provide reliable answers if they have sufficient power. For instance, in pregnancy and childbirth, the most robust outcome measure (maternal or fetal death or severe disability) is rare, thus sufficient power can only be obtained by studying a large number of women and their offspring. Although one could, in theory, perform single-center studies that run for a long period of time, this has the disadvantage that medical developments may make the clinical question of the study irrelevant.

Furthermore, it has become clear that disability may take some time to appear and that interventions may have different effects on surrogate short-term outcomes such as gestational age at delivery and neonatal health in hospital compared with the effects on long-term outcomes such as cerebral palsy. A good example of the latter issue occurred in the ORACLE studies, in which publication of the follow-up of children at 7 years indicated harm associated with antibiotics administered to the mother in the study group with intact membranes, whereas the initial reports indicated no difference in fetal outcomes between placebo and treatment with antibiotics in this study group. 4-6

Keywords
► Global Obstetrics Network
► multicenter studies
► trial collaboration
► maternal–fetal medicine and obstetrics

Abstract

Large clinical studies provide information and insight that are used to develop clinical guidelines. In view of the large sample sizes needed, many researchers have initiated multicenter studies. In some situations, the activities of these groups have led to networks, through which multiple trials have been executed over a longer period of time. The Global Obstetrics Network (GONet) was formed to link the different types of networks. The GONet mission is “to provide a forum for international interaction and collaboration among groups that perform clinical trials and observational studies in maternal fetal medicine and obstetrics.” The purpose is to foster communication between groups to improve ongoing and future trials. This will open new avenues for cooperation in the design and conduct of large international trials, in seeking funding, and in highlighting evidence. The expectation is that this will lead to better studies and more efficient use of resources and minimize duplication. Furthermore, the group will provide insight and camaraderie, cooperate on data elements to allow future collaborations, and identify and highlight the pressing issues in maternal–fetal medicine. Here we describe the GONet mission, its objectives, structure and function, current collaborators, and plans for the future.
Another issue is the need to study a sufficiently large sample to produce results that can be extrapolated to populations outside the study sample. Low participation rates can result in studies not reaching their planned numbers, and as a consequence widespread uncertainty about conclusions may arise. The problem has been recognized before: in 1979, Lasagna commented on a trial where only 100 of 8027 possible candidates participated. This led to what is now popularly called Lasagna’s law: in any trial, the incidence of the disease studied will be reduced to 10% of the original estimate.

One way to accrue sufficient patient numbers in trials is to employ a multicenter design; this requires collaboration between researchers and an agreement to follow the same protocol. Multicenter trials tend to be more expensive than single-center trials, as they are generally monitored more closely for protocol adherence. Raza et al. found that in the past 30 years there has been an increase in published multicenter RCTs from 13% in 1975 of all RCTs to 24% in 2005. Multicenter RCTs received external funding (odds ratio = 2.4; 95% confidence interval 1.7 to 3.5) more often than single-center RCTs. This illustrates the increasing complexity of medical research necessary to underpin evidence-based practice.

International Collaborative Research Groups and Networks

In view of the need for multicenter RCTs, there have been initiatives to collaborate in clinical research in many countries. An example in the United States is the Maternal Fetal Medicine Units (MFMU) Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD; http://www.bsc.gwu.edu/MFMU). The NICHD established this network in 1986 to conduct randomized trials and observational studies in perinatal medicine to improve adverse pregnancy and infant outcomes. Currently, the MFMU Network consists of 14 university-based clinical centers performing more than 160,000 deliveries per year and an independent data coordinating center. Membership in the MFMU Network is determined by open competition every 5 years. More than 40 trials and observational studies have been conducted, the results of which have been incorporated into clinical recommendations and guidelines. Since the initiation of the MFMU Network, other obstetric networks and study groups have been created by NICHD to address specific issues.

In Canada, only a handful of the 16 university-based centers for maternal–fetal medicine take the role of leading clinical trials (Montreal, Toronto, and Vancouver in particular). The Center for Mother, Infant, and Child Research in Toronto is one unit that conducts international large multicenter trials, such as the often-cited Term Breech trial. Perinatal and neonatal medicine in Canada is supported by the infrastructure and data of the Canadian Perinatal Network, Canadian Neonatal Network, and Canadian Neonatal Follow-up Network.

The United Kingdom also has a track record of testing obstetric interventions in multicenter clinical trials, with central support from the National Perinatal Epidemiology Unit in Oxford. Recently, the National Institute for Health Research has developed topic-specific, primary care, and comprehensive research networks to provide infrastructure for high-quality research involving National Health Service patients. The Reproductive Health and Childbirth network supports all clinic-based studies in obstetrics and gynecology in the United Kingdom (current studies > 120). For example, the network is currently supporting the United Kingdom Medical Research Council–funded OPPTIMUM trial (progesterone prophylaxis in women at risk of preterm labor). There are also several clinical study groups in obstetrics supported by the Royal College of Obstetricians and Gynaecologists. These study groups support the development of trials for funding and may also recommend to government priorities for funding.

In Australia and New Zealand, there has been a strong tradition of large, collaborative multicenter trials in obstetrics. Following the completion of an early study, the need for formalization was appreciated and the IMPACT (Interdisciplinary Maternal Perinatal Australasian Clinical Trials) Network formed. IMPACT is a multidisciplinary group that meets annually to identify research priorities and discuss protocols for studies in their planning stages.

The collaborative networks initiated in the United States, the United Kingdom, and Canada inspired clinicians and researchers in other countries to start similar initiatives. Two examples are the Dutch Obstetric Consortium and the Hong Kong Maternal Fetal Medicine Network. The Dutch Consortium, which was formed in 2004, now covers all 10 perinatal centers in the Netherlands (http://www.studies-obsbyn.nl). The Hong Kong Maternal Fetal Medicine Network was formed in 2009 by the collaboration of four of the eight public hospitals, led by the Chinese University of Hong Kong. The aims are to train maternal–fetal medicine subspecialists and to conduct large multicenter clinical and laboratory studies.

The Global Obstetrics Network

In 2010, representatives of the groups described earlier and other study groups conducting multicenter studies in obstetrics met to discuss the possibility of forming a global collaboration. As a result, the Global Obstetrics Network (GONet) was initiated to provide a forum for international interaction and collaboration among groups that perform clinical trials and observational studies in maternal–fetal medicine and obstetrics, identifying and highlighting the pressing issues in this research area.

The purpose of GONet is to foster communication between the groups to improve ongoing and future trials. We hope to open new avenues for cooperation in the design and conduct of large international trials, in seeking funding, and in identifying and highlighting the pressing issues in maternal–fetal medicine. The expectation is that this will lead to better studies and more efficient use of resources and minimize duplication. It is noted that some duplication of studies is important to lessen the chances of making a type 1 error and
to ensure generalizability; however, six studies on progesterone in twins or aspirin to prevent preeclampsia is probably not the optimal way to spend collaborative resources.

The members of GONet identified several areas to address. These include the following:

- Identifying aspects of maternal health that most urgently require clinical trials to establish best practice and prioritize these into a trial portfolio;
- Establishing processes by which the network can respond rapidly to emerging issues in maternal health;
- Developing a database of ongoing and planned studies;
- Setting up an education program for obstetric research (in doing so, we hope to build capacity for well-conceived and conducted research among young investigators);
- Defining study terms and (end point) definitions (for example, in cooperation with the Core Outcome Measures in Effectiveness Trials Initiative or the International Committee of Medical Journal Editors; defining variables and end points consistently will facilitate and enhance the integrity of meta analyses);
- Developing common protocols for some exemplar trials;
- Coordinating study protocols for individual patient data meta-analysis (even if two trials have different primary end points, for example, we can ensure both trials collect the same end points defined consistently);
- Facilitating the development, funding, and conduct of international, multicenter clinical trials.

After the first informal meeting in 2010, a small working group met in September 2010 at the World Health Organization (WHO) in Geneva. At this meeting, a charter and organizational structure was finalized. A board was formed with representation from the groups described above in Europe, North America, Australia, and Asia, in addition to a representative from The International Preterm Birth Collaborative, WHO, and the Cochrane Collaboration. Board members will be active for a period of 2 years.

The first general meeting was held at the Society for Maternal Fetal Medicine meeting in 2011. At the launch more than 100 researchers showed great enthusiasm for the initiative and discussed the structure of GONet as well as the aims including defining uniform end points for research, establishing a database of planned studies, performing individual patient data meta-analyses, and contributing to education.

Progress has been made toward these goals. A members’ Web site has been developed (www.globalobstetricsnetwork.org), including a database of ongoing/planned trials. The plan is to continue this activity in conjunction with the Global Alliance to Prevent Prematurity and Stillbirth. A collaborative individual patient data meta-analysis on progesterone in multiple pregnancies has been conducted, and there is the intention to do the same for studies on induction of labor in women with preterm premature rupture of membranes between 34 and 37 weeks.

A course on clinical trial design and conduct in obstetrics was organized by GONet members and conducted at the 2012 annual meeting of the Society for Maternal Fetal Medicine in Dallas, Texas. Further courses are planned in conjunction with two other international conferences.

A meeting with representatives from international funding agencies was held; we were encouraged to submit proposals for funding. To realize the goals stated, we are requesting funding support for infrastructure to enable communication and provide support. Two international offices, responsible for overseeing and managing the technical and financial functions as a whole will be founded, each led by an experienced researcher in maternal health, and will include an administrative post and a researcher with subject-specific expertise. One office will be in a developed country and the other in a developing country, to facilitate research collaboration worldwide.

Discussion

Multicenter trials have been well established for several decades in several countries around the globe. Some of the trial investigators have already set up international collaborations, resulting in studies where patients are recruited from all over the world. In our opinion, a combined approach for these activities would bring several improvements. First, a global cooperation like GONet could be a forum to exchange protocols, thus enabling uniform definitions of entry criteria and outcome. This will facilitate pooling of study results in meta-analysis and their implementation in clinical practice.

Second, the collaborative networks could contribute to a database of planned studies, not just at the start of the study, such as is done for one of the standard trial registries, but also at the moment when groups apply for funding for studies, or even at an earlier stage. This might avoid duplication of studies that are funded from collective resources in various countries.

The collaboration will also facilitate several forms of meta-analysis, such as prospective meta-analysis and individual patient data meta-analysis. In prospective meta-analysis, a plan for meta-analysis of individual studies is made before the start of the individual studies or while they recruit. In individual patient data, data of original studies are metaanalyzed on the level of the individual patient. This allows analysis up to the level of the homogeneous subgroup and allows the introduction of personalized medicine.

The collaboration may also result in studies on rare diseases, which need worldwide recruitment, or sample sizes that are too large to be funded from a single funding body. Funding bodies might collaborate by each supporting part of a trial.

Every trialist around the globe that is involved in multicenter trials can become a member of GONet. More information on GONet and registration can be found on our Web site: www.globalobstetricsnetwork.org.

GONet Board Members

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References
10. Thom EA, Rouse DJ; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. What we have learned about conducting randomized controlled trials in the NICHD MFMU network. Semin Perinatol 2003;27:253–260
15. Groom KM, Shennan AH, Jones BA, Seed P, Bennett PR. TOCOX—a randomised, double-blind, placebo-controlled trial of rofecoxib (a COX-2-specific prostaglandin inhibitor) for the prevention of preterm delivery in women at high risk. BJOG 2005;112:725–730