

Collaboration to Understand Complex Diseases Preeclampsia and Adverse Pregnancy Outcomes

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• Online Data Supplement

The strategy of intellectual collaboration has accelerated modern research and research success. Identified by Professor Robert Adams in 2013 as the Fourth Age of Research collaboration is evident through ever increasing numbers of international multicenter publications. These tend to provide positive benefits in terms of citation; indeed Universities with a lower percentage of home grown papers have higher research incomes.¹ The European Commission has placed collaboration at the heart of its research strategy and reported on the economic benefits. Emerging economies such as those of South America have also recognized the benefit of international collaboration.² Much of the effort has been bottom up, that is, through researcher led collaborations, such as in the field of genetics, for example, genomics. Cancer, diabetes mellitus, and Alzheimer disease research³ have all benefited through extensive collaborative efforts.

We have developed a consortium to emulate the best of this collaborative spirit, known as Global Pregnancy Collaboration (CoLab). CoLab, from its inception in 2010 has focused on adverse pregnancy outcomes and achieving a better understanding of their causes (online-only Data Supplement). Here, we review the pathologies we seek to understand and explain why better understanding mandates a global network of scientific and clinical experience. We present preeclampsia as a prototypical disorder but similar networks and collaboration are mandatory for understanding all human disease and, in particular, rare disorders. We highlight some of the challenges to collaborative studies, despite the overarching view, with supporting evidence, that this approach benefits all, and is to be encouraged. These challenges are not isolated to our discipline. We seek to bring attention to common hindrances, drawn from experiences within the CoLab consortium and suggest possible solutions.

Preeclampsia: Potential for Gain From Collaboration

Adverse pregnancy outcomes such as preeclampsia, pre-term labor, stillbirth, and fetal growth restriction continue to be major causes of morbidity and mortality for mothers and infants, particularly in low- and middle-income countries (LMIC). In high-income countries (HIC), empirical strategies have been moderately successful in palliating some aspects of morbidity, but even in HIC these conditions continue to plague pregnant women and their offspring. This, despite the fact, that technological and academic advances in bioscience have greatly increased our understanding of the pathophysiology of these disorders. In a recent article focused on preeclampsia, we asked the question, “If we know so much about preeclampsia, why haven’t we cured the disease?”⁴

Preeclampsia provides a typical example of a disorder in which research confined to small-scale studies, and geographical location has hindered successful understanding and progress toward treatment or cure. Over 2000 years ago, it was recognized that seizures that abated with delivery occurred in some pregnant women. This disorder, eclampsia was, until the beginning of the 20th century considered a pregnancy-specific seizure disorder.⁵ The discovery that these seizures were accompanied by the new onset of proteinuria, and elevated blood pressure led to the recognition that these signs preceded seizures (hence preeclampsia) and were associated with fetal and maternal death and morbidity, even without seizures. The first impediment to progress in preeclampsia research was the likely erroneous conclusion that these nonspecific criteria identified a single disorder. The clinical characteristics of preeclampsia are extraordinarily diverse. The syndrome presents sometimes as almost immediately life threatening, and at others as a slowly progressive disorder, usually occurring in the last few weeks of pregnancy but occasionally much earlier. Fetal growth restriction is also not a constant, occurring

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in about one third of cases. Furthermore, the epidemiological implications of the disorder are different depending on the clinical presentation. Overall, preeclampsia is associated with a 2-fold increase of later life maternal cardiovascular disease,⁶ whereas preeclampsia presenting before 34 weeks of gestation increases risk 8 to 10 fold.⁷ Laboratory findings are also widely variable. As we have recently reported this is partly because lack of standardization of method making difficult any comparison between studies,⁸ and attempts to predict preeclampsia with analytes measured in early gestation have not been clinically useful.^{9,10} Most analytes with promise are more predictive of early rather than late disease supporting the concept that preeclampsia occurring at these 2 time points is different.¹¹ However, the incidence of early-onset preeclampsia is low compared with late onset, raising questions as to the adequacy of power in small-scale studies. Furthermore, a characteristic of clinical trials attempting to prevent preeclampsia has been success of early interventions in small homogeneous populations and consistent failure in larger heterogeneous populations. Although most differences in outcome have been attributed to the sample size, a reasonable alternative is that success has occurred within homogeneous populations found in single centers, and failure has befallen multicenter trials with greater diversity of subjects.

Importantly, and fundamental to the principles of CoLab, the overwhelming majority of studies of adverse pregnancy outcomes are from HIC with little research in LMIC where most of the deaths attributable to preeclampsia occur and where causes could be different. Moreover, although efforts to transfer useful clinical and public health strategies from HIC to LMIC have met with some success, particularly in research settings, the ability to prevent, predict, and reverse these processes more broadly in any population has been minimally effective.

In recognition of the variants in preeclampsia that may not all share similar proximate pathophysiology, investigators have been becoming increasingly aware of the need to study homogeneous subgroups of subjects (although this remains far from a universal approach). The need for studies sufficiently powered to consider these individual subsets of patients is now self-evident. Moreover, meta-analysis of small-scale studies is fraught with problems of diversity in clinical and biochemical data and even different criteria for diagnosis. A global, cohesive approach is required. Only then will similarities and differences between proximate causes and pathophysiology of preeclampsia be characterized with confidence, and a stratified approach to management and treatment developed.

The Global Pregnancy Collaboration

The CoLab is a consortium of investigators committed to rectifying deficiencies in finding clinically relevant solutions to the problem of adverse pregnancy outcomes and transferring this knowledge to LMIC (Data Supplement). As highlighted in the recent literature,^{12,13} collaboration is essential both from an intellectual standpoint and through sharing data and biological samples because we are now aware of the major causes of adverse maternal and infant outcomes demonstrate a higher order of complexity than ever previously imagined. The current concept of preeclampsia's pathophysiology, which

invokes inflammatory and immunologic origins, is provocative of different origins in different settings. We must begin to appreciate that the imbalance between the research effort (probably <1% of the total), and maternal deaths from preeclampsia (>99%) in LMIC is unlikely to reduce the global burden of this disease. In LMIC differences in socioeconomic support, infectious diseases and sexual practices to mention only a few important differences from HIC could have major influences on those pathophysiological pathways repeatedly trodden by preeclampsia researchers in HIC. These likely but untested, differences demand a collaborative effort. Such complexity requires intellectual collaboration and diversity of clinical data and biological sample banks. There is a need, too, for larger scale prospective collaborative global studies, homogeneity of protocols, and standards for definition of clinical end points. This requires sharing and altruism. Intellectual collaboration will facilitate prioritization of targets but also provides the intellectual ferment for innovative thinking. Large data and sample sets will aid in the recognition of subtypes and pathophysiological pathways and test the global generalizability of predictors and disease markers. The use of these existing large data and biobanks in HIC and their establishment in LMIC should speed discovery, a vitally important goal for LMIC.

Although our efforts have to date focused on preeclampsia, the challenges facing collaborations such as ours apply to translational research in the wider field of obstetrics and to other disciplines in general.

The Challenges

Mindset and Ownership

A major challenge lies in the mindset of investigators. Scientists are motivated by incentives that promote individual idea ownership and a system of "winner-take-all". Continued employment, promotion and tenure—the coin of the realm—are afforded to those who gain independent grant funding, build a portfolio of first and last authorships, and own potentially marketable patents. The last of these, ownership, is also increasingly sought by research universities strapped by shrinking sources of extramural revenue, but its value in a world of international multiownership becomes increasingly meaningless, when income must be split between all parties. Professor Adams writes,¹ *First, in this age of big data that are internationally shared, the question will be who has the skills to exploit knowledge assets fastest, not who owns them.* However, the frame of idea of ownership and the delivery of riches to one or a few, despite some progress remains a deterrent to group science. It also ignores the fact that almost all ideas are built on the ideas of others. Gain for the institution and the individual is valued more than societal good. An alternative mindset is that science must serve society and researchers must pay back the subjects who volunteered to be involved in their research. Such a frame would imply that patents and first author publications are less important than the public good a scientist does.

Nonetheless, issues of credit, authorship, and inclusion of junior investigators to guarantee sustainability of our effort, and the field writ large must be addressed. This requires

institutional reorientation toward formal recognition of collaboration, which should be an identifiable metric of success. This applies as much to funding awards as it does to authorship. In CoLab, agreement about authorship is determined before the study outcome is known. Although self does not predominate, our policy of fair sharing of authorship and discovery remains key to satisfying the present, and to our thinking, outdated needs of our Universities. Maybe those who join this consortium self-select in terms of an international and cooperative mindset, and recognition that the gains are ultimately greater. For the individual member, trust must also be built by way of fair and inclusive rules and by means of investigator interactions through conference calls, committee work, and face-to-face meetings. This is feasible.

Unified Data Sets

One common issue we face is the inconsistency in the database data dictionaries used from one group to another and from one country to another. We have recommended that a minimal and identical data set should be a common goal in conducting future preeclampsia studies, particularly in LMIC.⁸ Over and above this, a more complex, yet standardized data set should be collected where practically feasible. Furthermore, there should be agreement on gestational ages for collection of biological samples. We propose that longitudinal clinical variables and samples be collected, when feasible, before disease onset to facilitate prediction strategies, and that samples be collected at the time of disease to advance identification of sub groups. State of the art sample collection methodology demands rigorously applied Standard Operation Procedures for sample handling, storage, and custodianship. Few collaborations have achieved this to date but we have learnt from the successful screening for pregnancy end points (SCOPE) consortium, a visionary prospective study, which recruited >5000 nulliparous women from 6 centers in 4 HICs in northern and southern hemispheres, all with the same protocol and a shared Internet database, and studied longitudinally. SCOPE to date has published >30 papers on preeclampsia and other pregnancy outcomes, the most cited of which receiving the *Hypertension* accolade as top clinical science paper of the year (2014).¹⁴

Even if the same data are collected by centers, enormous challenges are introduced in retrospective collation because of the multitude of different databases and formats of storage. Frequently, this places unnecessary limits on the information achievable, much being wasted through incompatibility. CoLab recently completed a study of angiogenic factors measured during pregnancy in 28 centers around the world; the stimulus being recognition of a role in the pathogenesis of the disease and the value of measurement of placentally derived angiogenic factors in preeclampsia prediction and diagnosis. Results from >16 000 pregnancies were used to interrogate questions about the pathophysiological role and predictive power of these analytes in preeclampsia. Despite the fact that the angiogenic factors were measured on disparate analytic platforms, merging was feasible with appropriate statistical adjustments for the different assays used.¹⁵ By far, the greatest challenge lay in merging the clinical data sets from participating centers. This took >2 years. With the

benefit of hindsight, planning and prospective collection of standardized data among the international obstetrics community delay, not to mention associated costs could have been avoided.

Organization and Financial Support

Meeting the challenges of collaboration and standardization requires organization and financial support. Databases must be aligned, samples made available and shipped, and appropriate projects must be selected and approved. None of the efforts come without expense. Establishment and maintenance of databases and biobanks as well as labor and related expenses for aliquotting, cataloging, retrieving, and shipping samples as well as linking with clinical data all require financial support. This is not easy to achieve. Consortium members can include these costs in all applications for funding, but funders, especially those who have supported development of prospective population cohorts should be encouraged to provide continuing support for these infrastructure costs within a given country, such as provided by the UK Medical Research Council.¹⁶

Legal Burdens and Bureaucracy

Perhaps the most potentially avoidable challenge is bureaucracy. The academic community is united in a collective frustration arising from the administrative requirements necessary for sharing data and biological samples between institutions.^{12,17} Certainly, it is mandatory to protect the interest of the women who provide their samples in accordance with their wishes. However, it is also important to recognize our responsibility to the same subjects to maximize the impact of their efforts by efficient and timely use of their data and biological contributions. Relevant to this topic is that because of changes in ethical requirements, many older samples are not supported by the specific consents now required for the sharing of samples. Beyond ethical considerations are the administrative and legal requirements related to intellectual property and legal liability risks. It is our experience and that of others, that these considerations present the greatest impedance to collaboration. A survey of CoLab members revealed delays of as much as 1 year in implementing collaborative efforts. Cited were the innumerable exchanges between technical offices at the different center institutions, arising in part from different legal expectations but more often because of one institution's difference in interpretation of the wording in material transfer agreement (MTA) forms used by the other. In the SCOPE consortium, more than a year's delay was incurred as MTA's went back and forth between the Universities and a commercial partner before analysis of samples could begin. Some institutions require an MTA between the hospital obstetrics unit and academic clinical obstetrics department, although the staff is one and the same, and the samples from research studies are stored in freezers in the clinical unit. Of the many black holes of communication between technical offices and academics, staff shortages have been frequently cited as a reason for delay. An extreme example of collaborative inertia lies in the countries that prohibit transfer of any biological materials beyond their borders. It is imperative that international efforts address these issues.

Meeting the Challenges

Mindset and Ownership

As noted above, the major objective of the Global Pregnancy Collaboration is to facilitate collaboration and sharing. We have made several contributions and continue to work with other groups to achieve this goal. Our first efforts were to develop a system that would encourage sharing by existing major databases and biobanks. Our members represent the majority of the world's largest data and biosample collections in preeclampsia research (Table S1 in the online-only Data Supplement). The issue of changing mindset has been less than expected. Investigators, we think, have an obligation to "get into the shoes" of patients to appreciate the need to maximize efficiency and effectiveness of the data so willingly volunteered. This should promote a willingness to forego some credit and control to further collaboration and large group attribution. Training collaborators by example has been one approach facilitated by our annual investigator meetings, for example, we demonstrate how much a single biospecimen collection and data set can be underexploited if not shared, and thereby jeopardize relevant outcomes.

Membership and participation has been greatly facilitated by encouraging elective collaboration rather than mandatory contribution. When samples or data are requested from CoLab members, the centers have the choice of participating or not. However, should even the majority of centers decline participation if sufficient material is available from those electing to participate, the request is granted and CoLab provides oversight, infrastructure and if necessary financial support to participants. Members providing samples or data are true collaborators and serve on the Protocol Committee for the study. This means participating in study design, data analysis, and eventual authorship of publications, with the inclusion and ordering of names agreed on early in article discussions. This approach has been successful for the limited number of groups involved (Table S2), but the eventual widespread success will require a more general shift in attitudes toward data ownership versus data custodianship.

Data and samples are always a result of intense labor and investments by resources. They could not exist without the effort of researchers, funders, and donor patients. It is extremely relevant that the sharing of data and biospecimens should reflect intellectual contributions through shared rules of authorship and intellectual property rights, and also institutional and funders contributions. Recognition of the bioresource and of the effort paid by the institution can occur at different levels from authorship to citation of the bioresource through the bioresource impact factor.¹⁸

Unified Data Sets

CoLab has also made progress in our efforts to standardize data fields and data format. Last year, we published a list of data that we suggested should be collected in all studies of preeclampsia (minimal data set) and an expanded list to be used should financial considerations permit (optimal data set).⁸ This has been well received by the research community. More recently, we embarked on a project that we hope will address the issues of data formatting. We are developing a

web-based preeclampsia database, modified from the SCOPE database, which will be available to investigators worldwide. The generous sharing by Professor Robyn North and the SCOPE consortium, who developed the database, exemplifies the spirit of CoLab. The database will be appropriate for both observational and clinical trials with a module for biosample inventory. It will have the facility for the addition of study-specific fields and will be available online for a nominal fee that can be waived for appropriate investigators (eg, LMIC or early career investigators). Access will also be provided free of charge for a version suitable for download on local computers. The data will remain the property of the investigator using the database. However, if (when) data sharing is elected, merging of the different studies will be almost instantaneous, although there remains the need for constant monitoring during collection to ensure consistent standards. To that end, a standard operations procedure manual will be made available and training, if necessary, provided.

This would seem a win-win situation for the individual investigator and the field of preeclampsia research. One of the major expenses of setting up a clinical study is establishing an appropriate database, and the advantage of standardized data format to the study of rare diseases has been emphasized.¹² Nonetheless, we think a major challenge to the usefulness of this database will be to encourage investigators to use this resource and to ensure that information of its existence reaches investigators worldwide. Throughout development, we have sought and continue to seek global opinions from researchers about the database content. We have aspired to increase awareness of this resource and to more generally maximize worldwide participation in CoLab. In designing the approach to the joint database, we focused on trust and credibility. We must convince investigators that the database is a service that will eventually facilitate data sharing but that they maintain control of the data and that access will depend on their previous permission.

Our inclusion of LMIC investigators in this venture is a deliberate effort to move data sharing and biobanks into these countries, that is in countries in which women are most commonly dying from the disease. We continue to make applications for extramural funding for LMIC projects, and will launch a seed-funding program for pilot studies of data and sample collection to demonstrate to funders the feasibility of projects in LMIC.

Although the standardization of procedures is highly desirable, we acknowledge that it is vitally important to be able to use existing resources. Although this presents a major challenge, harmonization of standards by comparing existing procedures, data, etc has been developed and used successfully.^{15,19} Different tools are available that can facilitate biobanking and collecting through set standards. We have also included as part of the database the possibility for a modest fee to work with the database administrators to standardize existing databases.

Organization and Financial Support

We have established in CoLab the nucleus for the administrative structure necessary to facilitate data and biosample sharing and foster intellectual collaboration. We have assembled 34

centers from Europe, North America, South America, Africa, and Asia (Table S1) and an Executive Committee guides activities. Although not extensive, we have acquired funding adequate to enable a yearly face-to-face meeting of the full membership and monthly WebEx communication for intellectual interactions and prioritization of projects. Projects are provided with communications support and when necessary, coverage of the costs of shipping samples. We request that investigators who are seeking extramural support approach us before grant submission. CoLab's modest infrastructure expenses are then built into the grant budget and samples earmarked for the study pending the funding decision. To bolster the application, letters of support are provided to the grant seeker. CoLab membership enables institutions to apply for access to all shared resources. Any other investigator may also apply for the use of CoLab resources with sponsorship by a CoLab member. We thereby encourage the use of CoLab data and samples from any investigator worldwide while ensuring appropriate guardianship of these invaluable resources. This practice is not intended to be restrictive; should investigators not have a CoLab contact, and if the Executive Committee favorably reviews the project, an appropriate CoLab partner is afforded (Table S2).

Because the activities of CoLab progressed and expanded over the past 3 years, granting agencies have become increasingly aware of the power of collaborative research, yet infrastructure funding for collaborative efforts remains difficult to access. Because the research community becomes increasingly conscious of the importance and value of sharing resources, a degree of urgency must be transmitted to all national and international funding agencies that provision of the modest infrastructural support requisite for developing and maintaining shared databases, biobanks, and intellectual synergies will enhance discovery. Another major barrier would be overcome if national funding agencies agreed to partly fund the same studies on an international level, avoiding redundancy through repetition, and thereby reducing overall costs. Here, we applaud the activities of the Global Obstetric Network collaboration that seeks to form collaborative networks for clinical trials in obstetrics worldwide with liaison between funding agencies (<http://www.globalobstetricsnetwork.org>). CoLab is also moving toward providing a general point of entry where consortia with data or biosamples can register their study and CoLab can direct investigators to appropriate collaborators. An early online version of such a registry is available through the LINK registry (<http://www.linkregistry.org>).

Legal Burdens and Bureaucracy

As detailed above, institutional restrictions and diverse regulations severely hamper timely sharing. We encourage early dialog to circumvent international consortia legal and ethical issues. In creating a trusted environment in international sharing recognition, it is indeed best to formalize sharing through proper MTA or data transfer agreements. In fact, in some countries exporting biosamples or health-related data might even be prohibited unless special safeguards are in place such as proper codification, consent, and MTA that clarify the goal and the restrictions of a specific research project. Having an

appropriate MTA helps in ensuring that proper ethical and legal procedures are followed to protect patients and researchers in an international endeavor. There remains, however, a little common ground between institutional requirements.¹² Extensive literature and resources address ethical and legal issues related to sharing, and we welcome the movement toward adoption of an international code of agreement.^{20,21} MTA models proposed include sections in which it is possible to formalize the kind of recognition planned for every contributor, in accordance to the scientific input provided. Generic models of MTA ready to use along with instructions on how to use them for international sharing are available.¹² These could help in addressing some of the legal and ethical issues related to data and samples sharing, including issues of privacy and security in data and samples exchange, ethical requirements, etc.

Planning ahead facilitates overcoming these challenges. New strategies are ideally developed in advance to collect data and samples in the proper way. Standardized procedures are the gold standard for new collections. Often ethical and legal issues are not thought out ahead of the study, not planned well and, therefore, may fail. New technologies may also help in developing new strategies for ethically and legally fit policies for future uses. In fact, web-based dynamic consent has been tested and proved an effective method to deal with specific challenges for international consortia, such as re-consent, continuous information, etc.^{22,23} Models to address prospectively those challenges exist and shall be used. The development in advance of tools to address ethical and legal issues, such as online electronic consent, updates through newsletters, or individual updates mailing lists, have proven to be effective ways to avoid most of the challenge faced today by international consortia.

Nonetheless, we must deal with pre-existing data, samples, and consents and with an attitude of administrators that intellectual property protection and eliminating any risk to the organization are primary driving forces. Where possible and feasible, re-consent should be sought to assess properly existing limits and foresee further developments of research in the consent form. Ideally, consent should contain information on international sharing and foresee possible recontact. Where individual re-consent is not possible, ethical clearance can be sought through the involvement of patients organizations and ethical committees permission. In certain instances, it is possible to request the ethical board for a waiver of consent. Conditions for a waiver are usually complete anonymization (not possible for anyone to reidentify data)¹² of samples and data associated. Research should in those circumstances not be too distant from the original purpose. Appropriate MTAs will then ensure that restrictions are met by consortia partners belonging to different legislative frameworks.

Working With Commercial Partners

In addition to public and private research funding agencies, the pharma and diagnostics industry is also a potential funding source. The availability of samples for discovery of novel predictors, diagnostics, and mechanistic biomarkers has enormous potential value for industry in new test development and drug discovery. Although inappropriate to

request a fee for human samples, inclusion in the access fee a portion of the consortium's expenses is entirely appropriate. Collaboration with industry for definitive regulatory approval beyond screening is disappointingly often limited by practicalities. Because of the heterogeneity of the samples and different collection strategies of the various existing biobanks, it may well be impossible to satisfy regulatory requirements, although standardization for this purpose should be a future goal. There are special challenges. National and international requirements may vary for the type of consent required. Local ethical assessment is necessary to ensure oversight by authorities that the informed consent collected is appropriate for sharing data with industry. Nonetheless, the availability of samples for testing and screening would be another win-win situation for industry and the consortium.

Perspectives

The complexity of human disease, which is magnified with pregnancy complications requires big data to unravel pathophysiology and demands collaboration of investigators worldwide, including LMIC to understand and apply diagnostic and therapeutic strategies. We must rethink conventional approaches to assigning credit to individual studies and investigators. The needs of our patients and respect for participating subjects mandate the maximal use of the clinical information and analytes. The additional advantage of a more collaborative approach is invaluable intellectual interaction. We must also rethink standardization of data and data formats. Educating funding organizations and administrative agencies about the necessity to support and promote rather than inhibit synergies between existing and new prospective studies must be a goal of investigators. The challenges are not minor but the means and materials are at hand. In the end, all clinicians and scientists are committed to the eventual reduction of human suffering. We think collaborations such as CoLab offer a best hope for achieving this goal.

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