

# The International Network of Obstetric Survey Systems (INOSS): benefits of multi-country studies of severe and uncommon maternal morbidities

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## Conflict of interest

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## Abstract

The International Network of Obstetric Survey Systems (INOSS) is a multi-country collaboration formed to facilitate studies of uncommon and severe complications of pregnancy and childbirth. Collaborations such as INOSS offer many benefits in the study of rare complications. The use of uniform case definitions, common datasets, specifically collected detailed data and prospectively agreed comparative and combined analyses all add to the validity of studies and their utility to guide policy and clinical practice and hence improve the quality of care. Such multi-national collaborations allow for the conduct of robust studies less subject to many of the biases attributed to typical observational studies. For very rare conditions such collaborations may provide the only route to providing high quality evidence to guide practice. Clinicians and researchers conducting studies into rare and severe complications should consider working through a network such as INOSS to maximize the value of their research.

**Abbreviations:** INOSS, International Network of Obstetric Survey Systems.

\*INOSS member countries: Australia: Elizabeth Sullivan; Austria: Willi Oberaigner; Belgium: Sophie Alexander, Yvon Englert, Myriam Hanssens, Griet Vandenberghe, Virginie van Leeuw, Wei-hong Zhang; Denmark: Lotte Colmorn, Jens Langhoff-Roos; Finland: Anna-Maija Tapper, Mika Gissler, Maija Jakobsson; France: Marie-Helene Bouvier-Colle, Catherine Deneux-Tharoux, Gilles Kayem; Germany: Silvia Berlage, Nicholas Lack; Italy: Serena Donati; The Netherlands: Kitty Bloemenkamp, Timme Schaap, Thomas van Akker, Jos van Roosmalen, Joost Zwart; New Zealand: Claire McLintock; Norway: Iqbal Al-Zirqi, Babil Stray-Pedersen; Portugal: Teresa Rodrigues; Slovakia: Miroslav Borovsky, Alexandra Kristufkova; Spain: Vicenc Cararac, Francesc Figuro; Sweden: Pelle Lindquist; UK: Peter Brocklehurst, Marian Knight, Jenny Kurinczuk.

## Introduction

Finding appropriate evidence to guide policy and practice for rare diseases and severe complications is a challenge for the maternity field as well as other specialties. Notably, when dealing with severe complications, we are faced with several difficulties that can be an obstacle to conducting robust studies. The rarity of these conditions in high-income settings leads to several issues. When disorders are uncommon, it is difficult to obtain a sufficient number of cases to undertake adequately powered studies without conducting them over a long period of time. The validity of studies using historical data may be called into question by changes in management over the lengthy period of the

study. Randomized controlled trials are impractical to conduct when conditions are very rare, even if challenges surrounding consent can be overcome (1). These severe morbidities usually occur in emergency situations and thus retrospective studies may be made difficult by limitations of documentation surrounding emergency events, and the resulting information biases. Additionally, in an attempt to identify sufficient cases, routinely collected hospital data are frequently used. However, studies using routine data on births, hospitalizations or insurance claims often raise concerns around the quality of the data and the validity of the cases identified, due to the inclusion of false-positive cases and the exclusion of false-negative cases. Routine data also have limitations in the level of detail collected about

individual management strategies. This restricts the ability of studies to investigate variations in management practice where these occur.

## What is the International Network of Obstetric Survey Systems?

The International Network of Obstetric Survey Systems (INOSS) is a multi-country collaboration which was formed to facilitate studies of uncommon and severe complications in pregnancy and childbirth (2) and, through the dissemination of the findings, to advocate for best care for mothers. Current member countries include Australia, Austria, Belgium, Denmark, Finland, France, Germany, Iceland, Italy, the Netherlands, New Zealand, Norway, Portugal, Slovakia, Spain, Sweden and the UK. The advantages of working as a network can be summarized in three main areas:

### 1 Use of uniform definitions

Differing definitions used to conduct studies can have a significant impact on the study findings, not only on estimates of incidence but also in terms of identified risk factors. In addition, the inclusion of cases using different definitions may have an important impact on the assessment of the efficacy of different management techniques. An example of a disorder where this use of variable definitions may have a major impact is that of uterine rupture. Studies of uterine rupture report a very wide range of incidences. This was highlighted in a recent review from the Agency for Healthcare Research and Quality at the US Department of Health and Human Services (3). That review identified studies with incidence rates ranging from 2 per thousand to 4 per thousand deliveries, and noted the particular importance of using an anatomical definition of uterine rupture. In a number of studies, it was impossible to distinguish women with asymptomatic dehiscence from those with a true uterine rupture, which clearly has a considerable influence on the reported incidence and outcomes of the condition. Two recent studies from members of the INOSS network using an anatomical definition and specifically excluding asymptomatic dehiscence estimated incidences of 0.2 and 0.6 per thousand maternities, respectively (4,5). Several INOSS member countries are currently conducting prospective studies of uterine rupture using unified definitions, which will enable a multi-national comparison of incidences, risk factors and outcomes.

### 2 Use of common methodology

The methodology used to study any particular rare condition can have a major impact on the findings of each study. For example, a review of multi-national studies of amniotic fluid embolism showed clear differences in the

incidence rates estimated using different methodologies (6). Those using specifically collected data which included an element of case validation, thus excluding other diagnoses, in particular primary postpartum hemorrhage, estimated the lowest incidence rates (7,8). Other research which used routinely collected data to identify cases, estimated a much higher incidence of the condition (9,10). However, when further validation elements were introduced into the latter studies, much lower estimates of incidence were obtained (11–13), the incidences being more comparable to estimates from studies using specific data collection. Specific data collection through a network such as INOSS enables the use of a clear case definition and agreed diagnostic and exclusion criteria, thus minimizing the risk of including false-positive cases in any study.

### 3 Use of specific data collection tools

Studies using routinely collected data have the advantage that the data are generally easily available, and therefore the studies may be quick and relatively inexpensive. However, these studies are limited by the number of data items that are included, and will inevitably lack detailed information about clinical management. Members of the INOSS network harmonize not only the definitions used to identify cases but also the variables collected, including the addition of specific detailed questions about management and outcomes. This allows research questions to be addressed which could not be investigated using most routinely collected data. INOSS member countries have generated evidence to inform aspects of management of many severe pregnancy complications (14–17).

The collection of these detailed data also allows for in-depth between-country investigation of variations in incidence and management. A comparison of eclampsia in the Netherlands and the UK highlights this. The incidence in the Netherlands was estimated to be 5.4 per 10 000 deliveries, twice the UK rate of 2.7 per 10 000. Detailed comparison of the cases (18) showed that management of cases in the Netherlands was in general less active, with lower rates of use of anti-hypertensive medication, longer delays before delivery of antepartum cases and less frequent use of magnesium sulfate. Guidelines for the management of hypertensive disorders have now changed in the Netherlands in an attempt to address higher rates of both mortality and severe morbidity from the condition. Maternal mortality from hypertensive disorders of pregnancy has dropped over the last seven years and the incidence of eclampsia is currently being studied by NethOSS, the Dutch INOSS member.

It is essential to recognize that within the INOSS network there are important links between routinely collected sources of data and specific data collection studies. For example, members of the Nordic Obstetric Surveillance

Study (NOSS) identify cases through specific reporting from hospital clinicians, but also check case ascertainment through their medical birth and hospital discharge registers, subsequently collecting more detailed data on additional cases identified through the registers about the case management and to confirm that the identified cases meet a robust case definition (19). This has the added advantage of enhancing case ascertainment, while maintaining uniform case definitions and allowing for detailed examination of management and is of particular value in countries such as the Nordic countries, where routinely collected data is generally very complete. In other countries where routine data are less robust, this approach may not be as valuable. In addition, linkage between the Nordic medical birth registers and bio banks increases the potential of research activities, which combine epidemiological and biological data for these rare serious obstetric complications (20).

### **What are the added advantages of a multi-country network over networks within individual countries?**

Studies from INOSS members have clearly shown the advantages of national networks of clinicians contributing to studies of uncommon and severe pregnancy disorders (14–17). However, multi-national studies using unified definitions and methodology can provide added benefits. Multi-national studies provide a clear advantage in terms of the number of cases which can be included in any study. When considering a very rare condition such as pulmonary vascular disease in pregnancy, which may affect as few as one in every 100 000 women delivering, even in a country with a large maternity population a study will only identify 5–10 cases per year. In smaller countries there may not even be one case per year. By working within a multi-country network, a study of only two years may identify up to 50 cases and enable more precise estimates of outcomes in the context of modern obstetric care as well as an accurate description of current obstetric management.

Within individual countries, management of particular conditions may be fairly uniform, informed by national guidelines, training or simply established practice. There is thus no scope to compare the outcomes of different management strategies. Across different countries, however, management may vary considerably, even where health systems are similar, and this allows for investigation of any association between particular treatments and disease outcomes. A multi-country network also facilitates educational co-operation where differences and similarities of treatment guidelines can be discussed. In the INOSS comparison of eclampsia in the UK and the Netherlands

described above (18), it was clear that anti-hypertensive treatment guidelines were very different between the two countries. Comparison of the data about eclampsia cases between the two countries suggested that this may have had a negative impact on the outcomes of women with eclampsia in the Netherlands.

A further advantage of multi-country comparisons is the ability to investigate different risk factors. The risk factor profiles of different populations of pregnant women may vary considerably from country to country, in terms not only of demographics such as ethnic group and age but also of other factors such as maternal socio-economic position and obesity, as well as medical factors such as prior delivery by cesarean section. Multi-country comparisons allow for an investigation of the impact of these differing risk factor profiles; for example, there is a wide variation in the rates of peripartum hysterectomy across INOSS countries. We hypothesize that this may be explained, at least in part, by different primary cesarean section rates (21). In a direct comparison between Slovakia and the UK, data suggested that variation in management of postpartum hemorrhage may also partly explain a difference in hysterectomy rates (22). A comparison of pregnant and postpartum women admitted to critical care with influenza A(H1N1) in the UK, Australia and New Zealand showed that there was a significantly higher risk of admission to critical care in Australia and New Zealand than in the UK, possibly because women admitted in Australia and New Zealand were significantly more likely to have a pre-existing medical condition, a known factor associated with poor outcomes from influenza A (H1N1) (23). In addition, women in Australia and New Zealand were less likely to receive antiviral treatment than were women admitted in the UK, potentially accounting for the higher incidence of severe disease.

A final important advantage of multi-national studies is the ability to investigate the replicability of observational findings across different populations. Observational studies are not able to demonstrate causality; however, replication of the findings across similar populations alongside biological plausibility of associations make the case for causality of those associations stronger, thus robust meta-analysis of multi-national studies of rare and severe disorders of pregnancy will clearly add to the evidence base. The INOSS collaboration aims to facilitate such robust combined analyses.

### **Future directions**

Collaborations such as INOSS offer many benefits to the study of rare and severe complications in pregnancy. Uniform case definitions, common datasets, specifically collected detailed data, and prospectively agreed comparative

and combined analyses all add to the validity of studies, the ability to generate new hypotheses, and their utility to guide policy and clinical practice. Such multi-national collaborations allow for the conduct of reliable studies less subject to many of the biases attributed to typical single-center observational studies. For very rare conditions, such collaborative studies may provide the only route to high quality evidence to guide practice. Clinicians and researchers interested in conducting studies into rare and severe complications should consider working through a network such as INOSS to maximize the value of their research. Our vision for the future is that care should be evidence-based not only for women with common obstetric conditions, but also for those affected by very rare and severe complications, facilitated by simultaneous network-wide INOSS studies. The challenge to achieve this goal lies in obtaining funding to conduct such studies; we advocate that national and international funding bodies recognize the added benefits of multinational collaborative research into uncommon, severe complications of pregnancy and delivery and prioritize such projects accordingly.

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