

# Outcomes in mothers with rheumatic diseases and their offspring workshop

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## ABSTRACT

This conference report describes six presentations that were given during a Canadian Institutes for Health Research-funded workshop. The goal of the workshop was to discuss key knowledge gaps in the study of outcomes in mothers with rheumatic diseases and their offspring. Presentations focused on epidemiological and methodological issues associated with the reproductive and perinatal health of women with rheumatic diseases. Discussions of relevant recent research allowed for discovery of potential data sources that could facilitate interdisciplinary research and created the opportunity for future collaborations.

## INTRODUCTION

For years, young women with rheumatic diseases were often counselled to avoid pregnancy because of the potential for adverse outcomes. For women with SLE, specific concerns included pregnancy-related disease flares, thrombotic events and preeclampsia (PE). In addition, there has traditionally been concern of an increased risk of miscarriage, stillbirth, low birth weight, preterm birth and neonatal death. In the last 20 years, many women with chronic rheumatic diseases, such as SLE, have had successful pregnancies, albeit with close monitoring and hopefully appropriate preventive therapies.

Emerging research has focused on assessing long-term health outcomes in children born to women with chronic rheumatic diseases. Some observational data suggest that children born to women with rheumatic diseases, including SLE, may have an increased risk of adverse outcomes that extend into childhood (including congenital heart defects (CHDs) and neurodevelopmental disorders) compared with children born to healthy women. Recognising the need for research and innovation in this area, EV and SB brought together a diverse group of health professionals who share an interest in

outcomes in mothers with rheumatic diseases and their offspring, with the collective goal of closing key knowledge gaps. Supported by a Canadian Institutes of Health Research's (CIHR's) Planning and Dissemination Grant, the 'Outcomes in mothers with rheumatic diseases and their offspring' workshop was organised for 25 rheumatologists, epidemiologists, clinicians, researchers and consumer advocates from around North America.

On 4 June 2015, EV and SB hosted their full-day workshop in Montreal. The workshop provided a forum for presentations on epidemiological and methodological issues associated with the reproductive and perinatal health of women with rheumatic diseases. Discussions of relevant recent research allowed for discovery of potential data sources to enhance research regarding mothers with rheumatic diseases and their offspring and facilitate interdisciplinary research across North America and beyond.

The programme included six presentations that provided an overview of current research activities in the field. The group was introduced to two interesting data sources: the Offspring of SLE mother's Registry (OSLER), a retrospective population-based cohort of children exposed and unexposed to women with SLE, and the Quebec Pregnancy Cohort (QPC), a population-based cohort that affords the opportunity to identify risks and benefits associated to medication use during pregnancy. Presentations also discussed the use of administrative data in the USA to study reproductive outcomes, prediction of placenta-mediated pregnancy complications, comorbidities of rheumatic disease pregnancies, neonatal lupus and statistical issues related to reproductive outcomes. A brainstorming session discussing key knowledge gaps related to research on outcomes in mothers with rheumatic diseases and their offspring, as well as the elaboration of future action points, concluded our workshop.



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## THE OSLER: AN OVERVIEW

EV discussed the OSLER cohort, the world's largest cohort of children born to women with SLE, which she created to evaluate the long-term health outcomes of SLE offspring. This retrospective population-based cohort study identified children born to women with SLE and children born to women without SLE using Quebec's administrative databases. EV summarised results from studies that used this unique data source, including findings that indicate that SLE offspring have more than a twofold increase in the risk of autism spectrum disorders,<sup>1</sup> CHDs<sup>2</sup> and stillbirths<sup>3</sup> compared with children from the general population. Other studies using this data source, including the study of increased direct healthcare costs associated with SLE pregnancies,<sup>4</sup> the increased risk of allergic conditions<sup>5</sup> and the increased risk of rheumatic and non-rheumatic autoimmune diseases in children born to women with SLE,<sup>6</sup> have been presented at conferences, such as the American College of Rheumatology Annual Meeting and the Laurentian Conference. EV recently updated the OSLER cohort data to extend follow-up time of existing subjects from 2009 to 2015 and obtain new deliveries. EV has also established a new cohort, the 'CHildren Of Rheumatoid arthritis mothers Database (CHORD)' (also using Quebec's administrative databases) to study the outcomes of children born to mothers with rheumatoid arthritis (RA) versus children born to unaffected mothers.

## INFERTILITY IN RA: A KNOWLEDGE GAP WORTH EXPLORING

BK focused her presentation on fertility in RA. She began her presentation by reviewing estimates of fertility and infertility in RA, highlighting the potential mechanisms of reduced fertility in RA and concluded by discussing data sources that may expand our ability to study fertility in RA. Her literature review indicates that historically women with RA have been considered to be less fertile and have fewer children in comparison to women without RA.<sup>7-11</sup> Diminished ovarian reserves<sup>12</sup> and inflammation<sup>13</sup> are thought to be a cause of infertility in RA while some studies have shown that a reduced family size was linked to personal choice,<sup>14 15</sup> reduced sexual desire<sup>16 17</sup> and disease-related factors affecting childbearing decision-making, including fatigue, ability to care, fear of genetic transmission to offspring and medication use.<sup>18-24</sup> BK provided information on an interesting pregnancy registry called the Better Outcomes Registry and Network (BORN). The registry collects fertility treatment, pregnancy, birth and childhood data on children born in Ontario to provide reliable, secure and comprehensive information on maternal and child health. The BORN Information System stores data related to every birth and young child in the province since 2012. Data are collected from fertility clinics, prenatal screening laboratories, specialised

antenatal clinics, midwifery groups, newborn screening laboratories and hospitals. Fertility issues in women with RA could be explored more extensively, notably through the support of comprehensive data sources such as BORN.

## PREDICTION OF ADVERSE PREGNANCY OUTCOMES AND PREVENTION WITH LOW-DOSE ASPIRIN

EB's presentation focused on the prediction and prevention of PE, a major contributor to maternal and fetal morbidity and mortality.<sup>25 26</sup> Numerous therapies<sup>27-36</sup> have been used as PE prevention strategies, but there has been a renewed interest in using low-dose aspirin to prevent PE, with meta-analyses demonstrating that low-dose aspirin initiated in the first trimester of pregnancy reduces the risk of PE by more than half compared with placebo.<sup>29-32</sup> Randomised trials demonstrate that low-dose aspirin improves uterine artery Doppler or blood flow when started in the first trimester.<sup>30 31</sup> Such results are likely to be the consequences of a significant improvement of deep placentation. Uncertainty remains regarding what the optimal dosage of aspirin should be; while most guidelines recommend dosages between 60 and 81 mg daily, about 30% of women do not respond to such dose and are said to be aspirin resistant.<sup>37 38</sup> It is likely that doses between 100 and 160 mg are required to significantly reduce PE and the other adverse perinatal outcomes. The next major step that needs to be taken for the prevention of PE is the identification of high-risk women who could benefit from aspirin started in early pregnancy, including determining if all pregnant women with SLE should be offered low-dose aspirin for the prevention of PE.

## ASSESSING PREGNANCY OUTCOMES IN WOMEN WITH RHEUMATIC DISEASE USING US ADMINISTRATIVE DATABASES

EC discussed the advantages and disadvantages of using administrative databases to answer research questions related to reproductive issues. The availability of administrative databases for research purposes has allowed for the conduct of observational studies of rare autoimmune diseases with larger sample size. However, the major disadvantage of administrative databases is the inability to apply classification criteria to validate cases as information on disease-specific classification criteria is often not available.<sup>39</sup> Disease activity and damage measures serve as important prognostic factors, particularly when studying pregnancy outcomes, but these data are often limited in administrative databases due to variation between patients. Another potential methodological issue relates to the timing of pregnancy onset, which is critical as the embryonic and fetal vulnerability to certain medications varies greatly by day or week of early gestation. Complications of early pregnancy (ie, occurring in the first trimester) can also be difficult to ascertain. While there is high level of accuracy associated with

identifying spontaneous abortions using International Classification of Diseases, ninth revision codes, pregnancy losses that occur before 15 weeks may not be captured as they usually do not require hospitalisation or even medical attention.<sup>39</sup> Despite these limitations, the use of administrative database to study pregnancy outcomes in women with rheumatic diseases avoids the limitations of tertiary care centre cohorts or voluntary registries. Improved diagnosis and procedure codes, the inclusion of additional variables such as laboratory and pharmacy data, and the ability to rapidly accumulate pregnancies in women with rheumatic diseases will allow for studies of outcomes unencumbered by selection bias, recall bias or biases introduced by changes in management of disease and pregnancy over years. It will allow for improved study of pregnancy outcomes as new strategies for managing both rheumatic disease and pregnancy evolve.

### DRUG EXPOSURES AND PREGNANCY OUTCOMES: THE QPC EXPERIENCE

AB discussed the QPC, which she created and directs, and on the potential and validity of using QPC as a research tool in perinatal pharmacoepidemiology. The cohort has already yielded crucial insights into drug use and health outcomes for both mothers and children.<sup>40</sup> The QPC was built by linking Quebec administrative databases, providing data on hospitalisations, outpatient visits, procedures and prescription filled by mothers and children. Her team also sent a self-administered questionnaire to a random sample of women to collect lifestyle information. The QPC includes data on all pregnancies of women covered by the Quebec provincial prescription drug insurance between 1998 and 2015. Date of entry in the QPC is 12 months prior to pregnancy, and women are followed during and after pregnancy; children are followed after birth up until 2015. The prevalence of prescribed medications before, during and after pregnancy was compared between time window.<sup>40</sup> Pregnancy outcomes were also estimated among pregnancies ending with a live-born infant. The QPC was described as an effective tool for the study of the risk and benefit of drug use during the perinatal period. This cohort has the advantage of including a validated date of pregnancy onset (based on last menstrual period) giving the possibility of assigning the gestational age at the time of maternal exposure.

### METHODOLOGICAL CHALLENGES IN PERINATAL EPIDEMIOLOGY

RWP focused on the challenges in perinatal epidemiology, specifically in relation to the study of pregnancy outcomes. Pregnancies can be clustered within women, and it is reasonable to assume that pregnancies within women are more similar than pregnancies selected at random. Thus, correlations between observations must be accounted for by using appropriate statistical

approaches. While methods to address clustered data are well-established,<sup>41</sup> these methods generally depend on the size of the cluster being independent of the outcomes.<sup>42</sup> With pregnancies, this is clearly not the case; a woman's gravidity may be high because she has had several children or because she has had several stillbirths. Twin pregnancies have obvious correlation that is much stronger than within-woman correlation overall. Several solutions to these problems have been proposed, including conditioning on first pregnancy, using all pregnancies but making appropriate assumptions, or using methods such as fixed-effects or self-controlled studies. A second source of debate in the perinatal literature is the choice of outcome and of denominator. When conditioned on birth weight or gestational age, selection biases can arise in associations between exposures and perinatal mortality; evidence of this appears with the so-called 'birthweight paradox',<sup>43 44</sup> in which an exposure that is associated with an increased risk of mortality overall appears to be protective at low birth weights. It has been shown that this paradox can be avoided by appropriate use of denominators. Small-for-gestational age (SGA) is frequently used as an outcome, as a proxy for intrauterine growth restriction. SGA, however, is defined as the lowest 10% of birth weights for gestational age. It must be remembered that this outcome is conditional on gestational age. Should an exposure cause both changes in growth and changes in gestational age, selection biases can arise.<sup>45</sup> Other work has shown similar results for other outcomes.<sup>46</sup> Finally, truncation and censoring are potential problems for studies of reproduction and fertility in particular. Left truncation of a cohort arises when follow-up starts after the index time and events between index time and the start of follow-up are not counted (eg, when pregnancies are followed starting at 12 weeks; events between conception (index time) and 12 weeks are missed). This can also occur in studies of time to pregnancy.<sup>47</sup>

### NEXT STEPS

After discussions related to presentations, through question and answer periods, the group broke off into small groups to brainstorm, guided by the question: what are the most important knowledge gaps related to research on outcomes in mothers with rheumatic diseases and their offspring? Workshop participants identified potential research questions that prioritised filling in existing knowledge gaps regarding outcomes for mothers with rheumatic diseases. The session also allowed for communication between different specialists, resulting in potential future collaborations. An action plan was organised to spur further research and dissemination activities by various stakeholders and agencies including consumer groups and others. The collaborations formed at the workshop facilitated the creation of a multidisciplinary group (with strong involvement of stakeholders and knowledge users) that works together to submit

applications for further peer-reviewed funding, to support research activities that will further advance knowledge relevant to outcomes for mothers with rheumatic diseases and their offspring. The brainstorming session discussing key knowledge gaps related to research on outcomes in mothers with rheumatic diseases and their offspring led to many future action points. These action points include elaborating a pragmatic trial on the use of aspirin to prevent placenta-mediated pregnancy complications in SLE, writing guidelines for rheumatic disease research related to reproductive issues and hosting webinars to maintain contact with the group. Funding has since been secured through another CIHR's Planning and Dissemination grant opportunity to support activities to discuss planning a pragmatic trial focusing on the potential benefits of aspirin use in lupus pregnancies.

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