Challenges in implementing Perinatal Clinical Studies in Canada: lessons learned

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Canada Research Chair in Perinatal Epidemiology
Department of Obstetrics and Gynecology,
Université de Montréal
CIHR sponsored Trials I have led

- The Amniotomy Trial (Fraser et al)
- VBAC Education Trial (Fraser et al)
- The Delayed Pushing Trial (Fraser et al)
- The Amniofusion Trial (Fraser et al)
- International Trial of Antioxidants in the Prevention of Preeclampsia (Fraser et al)
Trials where I’ve been co-Investigator:

- Structured Early Labour Assessment and Care by Nurses (SELAN) (Hodnett et al)
- TRIGR (Akerbloom, Knip, Dupré et al)
- Trial of Home versus Hospitalized Care for High Risk Pregnancy (Goulet)
- Quarité trial (ongoing) (Dumont et al)
- Quarisma (ongoing) (Chaillet et al)
‘Impossible to do a RCT of Amniotomy’: Emmanuel Friedman

Vol. 298  No. 16  EARLY AMNIOTOMY AND RISK OF DYSTOCIA IN NULLIPAROUS WOMEN—FRASER ET AL.  1145

EFFECT OF EARLY AMNIOTOMY ON THE RISK OF DYSTOCIA IN NULLIPAROUS WOMEN

WILLIAM D. FRASER, M.D., M.SC., SYLVIE MARCOUX, M.D., P.H.D., JEAN-MARIE MOUTQUIN, M.D., ANDRÉE CHRISTEN, M.SC., AND THE CANADIAN EARLY AMNIOTOMY STUDY GROUP

Abstract  Background. Early amniotomy has been advocated as a means of preventing dystocia, but its efficacy has not been studied prospectively. The purpose of this multicenter study was to determine whether routine early amniotomy reduces the risk of dystocia for nulliparous women in spontaneous labor.

Methods. We studied 925 nulliparous women in labor, who were stratified according to the degree of cervical dilatation (<3 cm vs. ≥3 cm) and randomly assigned to either early rupture of the membranes (amniotomy group) or conservative management of labor (conservative-management group). Dystocia was defined as a period of at least four hours after dilatation of the cervix to 3 cm had been reached during which the mean rate of cervical dilatation was less than 0.5 cm per hour.

Results. Intrauterine pressures shorter in the amniotomy group, and there was a trend toward less frequent use of oxytocin among the women assigned to amniotomy (36 percent vs. 41 percent; relative risk, 0.9; 95 percent confidence interval, 0.8 to 1.0). In a stratified analysis, the frequency of dystocia associated with amniotomy was reduced only among women with ≥3 cm initial dilatation. The cesarean-section rate was similar in the two groups (amniotomy, 12 percent; conservative management, 10 percent). There were no statistically significant differences between the infants delivered by the women in the two groups; the measures of an adverse outcome included admission to a neonatal intensive care unit, five-minute Apgar score below 7, and arterial cord-blood pH below 7.2.
# Results – Amniotomy Trial

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>AMNIOTOMY (N = 462)</th>
<th>CONSERVATIVE MANAGEMENT (N = 463)</th>
<th>RELATIVE RISK (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dystocia</td>
<td>155 (34)</td>
<td>207 (45)</td>
<td>0.8 (0.6–0.9)</td>
</tr>
<tr>
<td>Use of oxytocin</td>
<td>168 (36)</td>
<td>190 (41)</td>
<td>0.9 (0.8–1.0)</td>
</tr>
<tr>
<td>Type of delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>266 (58)</td>
<td>280 (60)</td>
<td>—</td>
</tr>
<tr>
<td>Vacuum or forceps</td>
<td>140 (30)</td>
<td>133 (29)</td>
<td>—</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>56 (12)</td>
<td>50 (11)</td>
<td>1.1 (0.8–1.6)</td>
</tr>
<tr>
<td>First stage of labor</td>
<td>38 (8)</td>
<td>31 (7)</td>
<td>1.2 (0.8–1.9)</td>
</tr>
<tr>
<td>Second stage of labor</td>
<td>18 (4)</td>
<td>19 (4)</td>
<td>1.0 (0.5–1.8)</td>
</tr>
</tbody>
</table>

*The conservative-management group was used as the reference group. CI denotes confidence interval.
## Analysis 1.2. Comparison 1 Amniotomy versus no amniotomy, Outcome 2 Caesarean section.

**Review:** Amniotomy for shortening spontaneous labour  
**Comparison:** 1 Amniotomy versus no amniotomy  
**Outcome:** 2 Caesarean section

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Amniotomy n/N</th>
<th>No amniotomy n/N</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
<th>Weight %</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Primiparous women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fraser 1991</td>
<td>8/47</td>
<td>4/50</td>
<td>2.13 [0.69, 6.60]</td>
<td>3.9 %</td>
<td></td>
</tr>
<tr>
<td>Fraser 1993</td>
<td>56/462</td>
<td>50/463</td>
<td>1.12 [0.78, 1.61]</td>
<td>49.9 %</td>
<td></td>
</tr>
<tr>
<td>Johnson 1997</td>
<td>19/346</td>
<td>10/254</td>
<td>1.39 [0.66, 2.95]</td>
<td>11.5 %</td>
<td></td>
</tr>
<tr>
<td>UK Amniotomy 1994</td>
<td>20/436</td>
<td>23/427</td>
<td>0.85 [0.47, 1.53]</td>
<td>23.2 %</td>
<td></td>
</tr>
<tr>
<td>Wetrich 1970</td>
<td>0/16</td>
<td>0/16</td>
<td>Not estimable</td>
<td>0.0 %</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1307</strong></td>
<td><strong>1210</strong></td>
<td></td>
<td><strong>88.6 %</strong></td>
<td><strong>1.13 [0.86, 1.49]</strong></td>
</tr>
</tbody>
</table>

Total events: 103 (Amniotomy), 87 (No amniotomy)  
Heterogeneity: Chi² = 2.41, df = 3 (P = 0.49); I² = 0.0%  
Test for overall effect: Z = 0.88 (P = 0.38)
# Meta-analysis of Amnioinfusion for Meconium Stained Liquor -12 RCTS

**Meta-analysis of the effect of amnioinfusion for MSAF on MAS**

<table>
<thead>
<tr>
<th>Trials</th>
<th>AI</th>
<th>Controls</th>
<th>Typical RR (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adams 1989</td>
<td>1 / 17</td>
<td>4 / 18</td>
<td></td>
</tr>
<tr>
<td>Sadovsky 1989</td>
<td>0 / 19</td>
<td>0 / 21</td>
<td></td>
</tr>
<tr>
<td>Wenstrom 1989</td>
<td>0 / 36</td>
<td>3 / 44</td>
<td></td>
</tr>
<tr>
<td>Llagan 1992</td>
<td>3 / 38</td>
<td>4 / 40</td>
<td></td>
</tr>
<tr>
<td>Macri 1992</td>
<td>0 / 85</td>
<td>5 / 85</td>
<td></td>
</tr>
<tr>
<td>Cialone 1994</td>
<td>1 / 47</td>
<td>8 / 58</td>
<td></td>
</tr>
<tr>
<td>Eriksen 1994</td>
<td>0 / 65</td>
<td>2 / 59</td>
<td></td>
</tr>
<tr>
<td>Spong 1994</td>
<td>3 / 43</td>
<td>1 / 50</td>
<td></td>
</tr>
<tr>
<td>Mahomed 1998</td>
<td>10 / 323</td>
<td>42 / 329</td>
<td></td>
</tr>
<tr>
<td>Moodley 1998</td>
<td>1 / 30</td>
<td>4 / 30</td>
<td></td>
</tr>
<tr>
<td>Alvarez 1999</td>
<td>1 / 53</td>
<td>0 / 62</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>24 / 918</strong></td>
<td><strong>79 / 959</strong></td>
<td></td>
</tr>
</tbody>
</table>
Unethical to do a RCT of Amnioinfusion?

Amnioinfusion for the Prevention of the Meconium Aspiration Syndrome

William D. Fraser, M.D., Justus Hofmeyr, M.D., Roberto Lede, M.D., Gilles Faron, M.D., Sophie Alexander, M.D., François Goffinet, M.D., Arne Ohlsson, M.D., Céline Goulet, Ph.D., Lucile Turcot-Lemay, M.D., Ph.D., Walter Prendiville, M.D., Sylvie Marcoux, M.D., Ph.D., Louise Laperrière, M.Sc., Chantal Roy, M.Sc., Stavros Petrou, Ph.D., Hai-Rong Xu, M.Sc., and Bin Wei, M.Sc., for the Amnioinfusion Trial Group*
<table>
<thead>
<tr>
<th>Outcome or Indicator</th>
<th>Amnioinfusion (N=986)</th>
<th>Control (N=989)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perinatal death or meconium aspiration syndrome</td>
<td>44 (4.5)</td>
<td>35 (3.5)</td>
<td>1.26 (0.82–1.95)</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>5 (0.5)</td>
<td>5 (0.5)</td>
<td>1.00 (0.29–3.45)</td>
</tr>
<tr>
<td>Moderate or severe meconium aspiration syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>According to clinical criteria‡</td>
<td>43 (4.4)</td>
<td>31 (3.1)</td>
<td>1.39 (0.88–2.19)</td>
</tr>
<tr>
<td>On chest radiography‡</td>
<td>19 (1.9)</td>
<td>13 (1.3)</td>
<td>1.47 (0.73–2.95)</td>
</tr>
<tr>
<td><strong>Neonatal resuscitation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oropharyngeal suctioning§</td>
<td>921 (93.6)</td>
<td>941 (95.3)</td>
<td>0.98 (0.96–1.00)</td>
</tr>
<tr>
<td>Laryngoscopy§</td>
<td>236 (24.0)</td>
<td>254 (25.8)</td>
<td>0.93 (0.80–1.08)</td>
</tr>
<tr>
<td>Suctioning of meconium below the cords</td>
<td>54 (5.5)</td>
<td>70 (7.1)</td>
<td>0.77 (0.55–1.09)</td>
</tr>
<tr>
<td>Any resuscitation</td>
<td>303 (30.7)</td>
<td>322 (32.6)</td>
<td>0.94 (0.83–1.07)</td>
</tr>
<tr>
<td>Oxygen only</td>
<td>205 (20.8)</td>
<td>213 (21.5)</td>
<td>—</td>
</tr>
<tr>
<td>Ventilation with bag and mask</td>
<td>79 (8.0)</td>
<td>90 (9.1)</td>
<td>—</td>
</tr>
<tr>
<td>Intubation with ventilation</td>
<td>19 (1.9)</td>
<td>19 (1.9)</td>
<td>—</td>
</tr>
<tr>
<td>Intubation of infant on departure from delivery room</td>
<td>7 (0.7)</td>
<td>7 (0.7)</td>
<td>1.00 (0.35–2.84)</td>
</tr>
</tbody>
</table>
### Table 3. The effect of AI on the risk of MAS

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard peripartum surveillance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sadovsky et al.\textsuperscript{35}</td>
<td>0/19</td>
<td>0/21</td>
<td>—</td>
</tr>
<tr>
<td>Wenstrom and Parsons\textsuperscript{37}</td>
<td>0/36</td>
<td>3/44</td>
<td>0.17 (0.01–3.26)</td>
</tr>
<tr>
<td>Macri et al.\textsuperscript{32}</td>
<td>0/85</td>
<td>5/85</td>
<td>0.09 (0.01–1.62)</td>
</tr>
<tr>
<td>Cialone et al.\textsuperscript{28}</td>
<td>1/47</td>
<td>8/58</td>
<td>0.15 (0.02–1.19)</td>
</tr>
<tr>
<td>Eriksen et al.\textsuperscript{29}</td>
<td>0/65</td>
<td>2/59</td>
<td>0.18 (0.01–3.71)</td>
</tr>
<tr>
<td>Spong et al.\textsuperscript{36}</td>
<td>3/43</td>
<td>1/50</td>
<td>3.49 (0.38–32.32)</td>
</tr>
<tr>
<td>Hofmeyr et al.\textsuperscript{30}</td>
<td>4/162</td>
<td>6/163</td>
<td>0.67 (0.19–2.33)</td>
</tr>
<tr>
<td>Moodley et al.\textsuperscript{34}</td>
<td>1/30</td>
<td>4/30</td>
<td>0.25 (0.03–2.11)</td>
</tr>
<tr>
<td>Puertas et al.\textsuperscript{17}</td>
<td>3/103</td>
<td>4/103</td>
<td>0.75 (0.17–3.27)</td>
</tr>
<tr>
<td>Fraser et al.\textsuperscript{16}</td>
<td>43/986</td>
<td>31/989</td>
<td>1.39 (0.88–2.19)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>55/1576</td>
<td>64/1602</td>
<td>0.59 (0.28–1.25)</td>
</tr>
<tr>
<td><strong>Limited peripartum surveillance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mahomed et al.\textsuperscript{33}</td>
<td>10/323</td>
<td>42/329</td>
<td>0.24 (0.12–0.48)</td>
</tr>
<tr>
<td>Rathore et al.\textsuperscript{18}</td>
<td>0/100</td>
<td>1/100</td>
<td>0.33 (0.01–8.09)</td>
</tr>
<tr>
<td><strong>Subtotal</strong>\textsuperscript{**}</td>
<td>10/423</td>
<td>43/429</td>
<td>0.25 (0.13–0.47)</td>
</tr>
<tr>
<td><strong>Total</strong>\textsuperscript{***}</td>
<td>65/1999</td>
<td>107/2031</td>
<td>0.47 (0.22–0.99)</td>
</tr>
</tbody>
</table>

\*χ^2 = 14.32, test for heterogeneity P = 0.07, I^2 = 44.1%.

\**χ^2 = 0.04, test for heterogeneity P = 0.85, I^2 = 0%.

\***χ^2 = 27.66, test for heterogeneity P = 0.002, I^2 = 63.8%.
A trial of KT for an approach to care that was not based on strong evidence:

Randomized controlled trial of a prenatal vaginal birth after cesarean section education and support program

William Fraser, MD, MSc,a Elizabeth Maunsell, PhD,b Ellen Hodnett, RN, PhD,c Jean-Marie Moutquin, MD, MSc,a and the Childbirth Alternatives Post-Cesarean Study Group
Quebec, Quebec, and Toronto, Ontario, Canada

OBJECTIVE: Our objective was to assess whether, for women with previous cesarean section, a prenatal education and support program promoting vaginal birth after cesarean delivery increases the probability of vaginal delivery.
Vitamins C and E for prevention of Preeclampsia

OBSTETRICS

An international trial of antioxidants in the prevention of preeclampsia (INTAPP)

Hairong Xu, MD, MSc; Ricardo Perez-Cuevas, MD, PhD; Xu Xiong, MD, PhD; Hortensia Reyes, MD, PhD; Chantal Roy, MSc; Pierre Julien, PhD; Graeme Smith, MD, PhD; Peter von Dadelszen, MBChB, DPhil; Line Leduc, MD; François Audibert, MD, PhD; Jean-Marie Moutquin, MD, MSc; Bruno Piedboeuf, MD; Bryna Shatenstein, PhD; Socorro Parra-Cabrera, PhD; Pierre Choquette, MD; Stephanie Winsor, MD; Stephen Wood, MD; Alice Benjamin, MD; Mark Walker, MD, MSc; Michael Helewa, MD; Johanne Dubé, MD; Georges Tawagi, MD; Gareth Seaward, MD; Arne Ohlsson, MD, MSc; Laura A. Magee, MD, MSc; Femi Olatunbosun, MD; Robert Gratton, MD, MSc; Roberta Shear, MD; Nestor Demianczuk, MD; Jean-Paul Collet, MD, PhD; Shuqin Wei, MD, PhD; William D. Fraser, MD, MSc; and the INTAPP study group
### RESULTS - INTAPP

#### TABLE 2. Primary outcomes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Vitamins C and E n = 1167</th>
<th>Placebo n = 1196</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH and its adverse conditions (^a)</td>
<td>118 (10.11)</td>
<td>122 (10.20)</td>
<td>0.99 (0.78–1.26)</td>
<td>.94</td>
</tr>
<tr>
<td>GH</td>
<td>253 (21.68)</td>
<td>249 (20.82)</td>
<td>1.04 (0.89–1.22)</td>
<td>.61</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>69 (5.95)</td>
<td>68 (5.71)</td>
<td>1.04 (0.75–1.44)</td>
<td>.81</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>1 (0.10)</td>
<td>0</td>
<td>–</td>
<td>.50</td>
</tr>
<tr>
<td>Diastolic pressure ≥110 mm Hg</td>
<td>32 (2.74)</td>
<td>27 (2.26)</td>
<td>1.21 (0.73–2.01)</td>
<td>.45</td>
</tr>
<tr>
<td>Systolic pressure ≥160 mm Hg</td>
<td>53 (4.54)</td>
<td>68 (5.63)</td>
<td>0.80 (0.56–1.13)</td>
<td>.21</td>
</tr>
<tr>
<td>Hematocrit &lt;24%</td>
<td>3 (0.26)</td>
<td>5 (0.42)</td>
<td>0.61 (0.15–2.57)</td>
<td>.50</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>3 (0.26)</td>
<td>6 (0.50)</td>
<td>0.51 (0.13–2.04)</td>
<td>.33</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>7 (0.60)</td>
<td>7 (0.59)</td>
<td>1.02 (0.36–2.91)</td>
<td>.96</td>
</tr>
<tr>
<td>Elevated liver enzyme levels (AST or ALT &gt;70 U/L)</td>
<td>9 (0.77)</td>
<td>7 (0.59)</td>
<td>1.32 (0.49–3.53)</td>
<td>.68</td>
</tr>
<tr>
<td>IUGR (&lt;3rd percentile) (^b)</td>
<td>18 (1.54)</td>
<td>15 (1.25)</td>
<td>1.23 (0.62–2.43)</td>
<td>.55</td>
</tr>
<tr>
<td>Perinatal death (^c)</td>
<td>5 (0.43)</td>
<td>1 (0.08)</td>
<td>5.12 (0.60–43.79)</td>
<td>.10</td>
</tr>
</tbody>
</table>
Lessons Learned from INTAPP

- Phase 3 Trials of medications where the biological mechanisms are not elucidated and where there are no strong phase 2 studies are at high risk of being negative trials.
- Biobanking is a complex endeavour
- Don’t take data quality for granted
- Don’t take competent financial management in centres for granted.
A trial of KT – a complex, evidence based intervention in a complex setting

Trials

Study protocol

QUARITE (quality of care, risk management and technology in obstetrics): a cluster-randomized trial of a multifaceted intervention to improve emergency obstetric care in Senegal and Mali

Alexandre Dumont*1,2,3,13, Pierre Fournier2,4, William Fraser1,3, Slim Haddad2,4, Mamadou Traore5, Idrissa Diop6, Mouhamadou Gueye7, Alioune Gaye8, François Couturier9, Jean-Charles Pasquier10, François Beaudoin1,3, André Lalonde11, Marie Hatem2 and Michal Abrahamowicz12

Address: 1Department of Obstetrics and Gynecology, Université de Montréal, Canada, 2Department of Social and Preventive Medicine, Université de Montréal, Canada, 3Research Centre of CHU Sainte Justine, Université de Montréal, Canada, 4CRCHUM Research Centre, Canada, 5Centre de santé de la Commune V [Health centre, Commune V], Bamako, Mali, 6Cabinet d'étude spécialisé dans la santé et l'action sociale (HYGEA) [Office
Lessons learned from Quarité

- Provides an opportunity to test the SOGC’s ALARM in an International setting
- Demonstrates the importance of professional organisations as partners in studying quality of care
- Cluster randomized trials are feasible in underresourced country settings
RAPID DETECTION OF GROUP B STREPTOCOCCI IN PREGNANT WOMEN AT DELIVERY

RAPID DETECTION OF GROUP B STREPTOCOCCI IN PREGNANT WOMEN AT DELIVERY

MICHEL G. BERGERON, M.D., DANBING KE, M.SC., CHRISTIAN MENARD, PH.D., FRANÇOIS J. PICARD, PH.D., MARTIN GAGNON, B.SC., MARTHE BERNIER, B.SC., MARC OUELLETTE, PH.D., PAUL H. ROY, PH.D., SYLVIE MARCOUX, M.D., AND WILLIAM D. FRASER, M.D.

ABSTRACT

Background  Group B streptococcal infections are an important cause of neonatal morbidity and mortality. A rapid method for the detection of this organism in pregnant women at the time of delivery is needed to allow early treatment of neonates.

were fatal.1 Infants who have such infections may require prolonged hospitalization, and those who survive may have mental retardation or visual loss. Among pregnant women, the prevalence of colonization with group B streptococci ranges from 15 to 40 percent.1 Women who are carriers are also at risk for severe in-
DSMB contribution

- Caffeine for Apnea of Prematurity (CAP) (Schmidt) (DSMB member)
- TIPP (Indomethacin) trial (Schmidt) (DSMB member)
- Canadian Oxygen Trial (Schmidt, DSMB Chair)
Summary: Lessons learned from Clinical Trials

- In TRIALS - Less is More (get primary objective) (INTAPP)
- Data management team is critical (INTAPP)
- TRIAL Coordinator is just as critical
- Be on top of ethical issues and anticipate results of parallel trials (INTAPP, COT)
Summary: Lessons learned

- Monitoring is critically important (Amnioinfusion, INTAPP):
  - don’t take data quality for granted,
  - don’t take competence in financial management for granted.

- Large trials on medical treatments for which there are no clear biological mechanisms are high risk of being negative trials (INTAPP)
Lessons learned

- Maintain close relationship with funding agency – keep them informed
- International Collaboration between Formal networks is a political challenge; international collaborations with scientists you can trust is the way to go, but infrastructure is fragile and can change rapidly.
Lessons learned trials

- Centres where prenatal obstetrical care is widely distributed in private clinics and where there is no common ‘Point of Contact’ in early pregnancy present a special problem.

- The infrastructure to support academic trials in the perinatal network in Canada is limited and depends on the good will of 1 or 2 individuals in most centres.
Cohort Studies

• Why cohort studies?
  ◦ Many important research questions cannot be addressed through clinical trials
  ◦ Ex. Ethical issues – cannot randomize women and children to certain exposures of interest
  ◦ Need life course approach with long term follow-up

• Unique challenges of cohort studies: confounding, measuring exposures and measuring confounders,
Project description
Funding Agencies

Health Canada

Santé Canada

CIHR IRSC

Ontario
Investigators

Principal Investigators:
Tye Arbuckle, PhD
Senior Epidemiologist & Research Scientist, Health Canada
William D. Fraser, M.D
Professor and Chair Obstetrics and Gynecology
Université de Montréal & CHU Ste-Justine

Co-investigators:
Jean-Philippe Weber, Melissa Legrand, Premkumari Kumarathasan, Renaud Vincent, Zhong-Cheng Luo, Adrienne Ettinger, Robert Platt, Grant Mitchell, Kevin Cockell, Maya Villeneuve, Sheryl Tittlemier, Pierre Julien, Denise Avard, Nick Hidiroglou, Hope Weiler, Alain LeBlanc, Site Investigators: Peter von Dadelszen (Vancouver), Michael Helewa (Winnipeg), Mathiew Sermer (Toronto), Warren G. Foster (Hamilton), Gregory Ross and Paul Fredette (Sudbury), Graeme Smith (Kingston), Mark Walker (Ottawa), Roberta Shear (Montreal), and Linda Dodds (Halifax).
Study coordinating centre

CHU Ste-Justine
3175 Côte-Ste-Catherine
Room 4986-B
Montreal (Qc)
H3T 1C5
CANADA

Tel.: (514) 345-4931 x 4151
Fax.: (514) 345-2195
Mirec.project@recherche-ste-justine.qc.ca
Objectives

- To obtain national-level data on maternal and neonatal exposure to priority environmental contaminants
- To obtain Canadian data on smoking behaviour and exposure to tobacco smoke (active and passive) in pregnancy
- To determine if heavy metal exposure is related to elevated maternal blood pressure, hypertension, altered sex ratio and fetal growth restriction
Objectives

- To obtain contemporary levels of priority environmental chemicals, selected nutrients and relevant immunoprotective endpoints in mature human milk.
- To obtain contemporary levels of maternal hair-mercury.
- To characterize dietary exposure of breastfed infants ages 2-8 weeks to allow for time-trend analyses for those analytes which were included in previous human milk surveys.
Study Design

- A National-level pregnancy cohort study, 10 Clinical sites across Canada
Participating Hospitals

01 BC Children and Women’s Health Centre, **Vancouver** - Dr. Peter von Dadelszen

02 University of Alberta, **Edmonton** – Dr. Suzanne Tough

03 St-Boniface Hospital, **Winnipeg** - Dr. Michael Helewa & The University of Manitoba

04 Mount-Sinaï Hospital, **Toronto** - Dr. Mathew Sermer

05 McMaster University Hospital, **Hamilton** - Dr. Warren Foster

06 **Sudbury** - Dr. Greg Ross /Dr. Paul Fredette

07 **Kingston** General Hospital - Dr. Graeme Smith

08 **Ottawa** General Hospital - Dr. Mark Walker

09a CHU Ste-Justine, **Montreal** - Dr. William Fraser

09b Jewish General Hospital, **Montreal** - Dr. Roberta Shear

10 IWK Health Centre, **Halifax** - Dr. Linda Dodds
Study population
Eligibility criteria

Inclusion criteria

1. The woman is pregnant between 6⁰/⁷ and 13⁶/⁷ completed weeks
2. Age ≥ 18 years
3. Speaks a language known by the medical staff (French or English)
4. Plans to deliver in a study participating hospital
5. The woman is able to understand and sign a consent form
Study Design

- 2,000 pregnant women recruited during 1st trimester
- Hospital-based sample
- Contacts during each trimester of pregnancy, delivery, and postpartum

- Prenatal visit 1: 6-13 wks GA
- Prenatal visit 2: 16-21 wks GA
- Prenatal visit 3: 32-34 wks GA
- Delivery
- Postpartum Day 1 or 2
- Post delivery (2-8 wks)
# Sources of Exposure

<table>
<thead>
<tr>
<th>Chemical Group</th>
<th>Biomarkers</th>
<th>Uses and Sources of Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metals/metalloids</td>
<td>Lead</td>
<td>Gasoline, paint, dust, drinking contaminated water</td>
</tr>
<tr>
<td></td>
<td>Mercury</td>
<td>Batteries, fluorescent light bulbs, fish consumption, dental amalgams</td>
</tr>
<tr>
<td></td>
<td>Cadmium</td>
<td>Pigments, municipal waste incineration, cigarette smoke</td>
</tr>
<tr>
<td></td>
<td>Arsenic</td>
<td>Pressure-treated wood, drinking contaminated water</td>
</tr>
<tr>
<td></td>
<td>Manganese</td>
<td>Burning of fossil fuels</td>
</tr>
<tr>
<td>Plasticizers</td>
<td>Bisphenol A (BPA)</td>
<td>Polycarbonate food containers, refillable water bottles, metal food and beverage cans, dental sealants</td>
</tr>
<tr>
<td></td>
<td>Phthalate metabolites</td>
<td>Polyvinyl chloride flooring, toys, detergents, personal care products, food packaging, dust</td>
</tr>
</tbody>
</table>
### Sources of Exposure

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<thead>
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<th>Chemical Group</th>
<th>Biomarkers</th>
<th>Uses and Sources of Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surfactants</td>
<td>Perfluorinated compounds (e.g., PFOS, PFOA)</td>
<td>Non-stick cookware, stain repellent furnishings, fast-food packaging</td>
</tr>
<tr>
<td>Pesticides</td>
<td>Organophosphate metabolites</td>
<td>Insecticides, food contaminant</td>
</tr>
<tr>
<td>Flame Retardants</td>
<td>Polybrominated diphenyl ethers (PBDEs)</td>
<td>Electronic equipment, furniture, construction materials, textiles, foods, house dust</td>
</tr>
<tr>
<td>Persistent Organic Pollutants (POPs)</td>
<td>Polychlorinated biphenyls (PCBs)</td>
<td>Industrial equipment, food</td>
</tr>
<tr>
<td></td>
<td>Organochlorine metabolites (e.g., DDE, aldrin, mirex)</td>
<td>Insecticides, food contaminant</td>
</tr>
<tr>
<td>Tobacco Smoke</td>
<td>Cotinine</td>
<td>Active and passive exposure to tobacco smoke</td>
</tr>
</tbody>
</table>
Nutritional status can play a role in altering absorption or susceptibility to toxicity of heavy metals:

- **Calcium**
  - Bone demineralization may be caused by insufficient maternal dietary sources of calcium

- **Iron**
  - Animal studies suggest that iron supplementation partially reduces the impaired fetal growth caused by cadmium

- **Selenium**
  - may also play an active role in maternal defence systems against the toxicity of metals and constituents of cigarette smoke
Other Data Collected

- **1\textsuperscript{st} and 3\textsuperscript{rd} Trimesters**
  - Smoking (active and passive)
  - Socio-demographics
  - Obstetrical history
  - Employment
  - Environmental exposures (work, home)
  - Physical activity
  - Sunlight exposure
  - Anthropometry
  - Blood pressure
- **Pregnancy outcomes**

*Why cohort studies?*
Challenges for MIREC

- Which are the priority chemicals to be measured?
- Which chemicals are likely to be stable over time and which chemicals need repeat measurement?
- Exploring disease mechanisms: if we find an association between an exposure and a trait, how do we select the pathways to be explored?
Réseau intégré de recherche en périnatalité du Québec et de l’est Ontario/
Integrated Research Network in Perinatology of Quebec and Eastern Ontario. (IRNPQEO)

Financé par les IRSC et la FCI dans le cadre du programme des Initiatives de recherche clinique en avril 2008
Researchers IRNPQEO

Chercheur Principal :
- Dr. William Fraser - Université de Montréal

Co-Chercheurs principaux :
- Lise Dubois - Université d’Ottawa
- Zhong-Cheng Luo - Université de Montréal
- Jacques Michaud - Université de Montréal
- Jean-Marie Moutquin - Université de Sherbrooke
- Gina Muckle - Université Laval
- Jean Seguin - Université de Montréal
- Margaret Somerville - Université McGill
- Jacquetta Trasler - Université McGill
- Richard E. Tremblay - Université de Montréal
Mission du réseau IRNPQEO et de son programme de recherche

Servir de catalyseur pour:

• Increase the quality of perinatal research in Québec and in Canada
• Train a new generation of researchers in a ‘4 pillar’ environment
• Create a provincial – regional model of perinatal research that will lead to innovations and that will ensure that care is evidence based.
Collaborations:

- RUIS Université de Montréal
  - 18 delivery units
  - > 27 000 deliveries / Year
  - **Expertise**
    - Genetics / epigenetics
    - Neurodevelopment
    - Cardiovascular disorders
    - Metabolism / growth
    - Psycho-socio economic
    - Environmental exposures
    - Artificial reproductive tech.

- CHU Ste-Justine
  - > 3 200 deliveries / Year
  - **Expertise**
    - Genetics / epigenetics
    - Neurodevelopment
    - Cardiovascular disorders
    - Metabolism / growth
    - Psycho-socio economic
    - Environmental exposures
    - Artificial reproductive tech.

- CHU de Québec (CHUQ)
  - > 6 200 deliveries / Year
  - **Expertise**
    - Genetics
    - Cardiovascular disorders
    - Placental disorders
    - Metabolism / growth
    - Health service
    - Environmental exposures
    - ERB base learning

- University of Ottawa
  - Perinatal Programme of Eastern Ontario
  - 3 500 deliveries / Year
  - **Expertise**
    - Epidemiology
    - Neurodevelopment
    - Health service
    - Artificial Reproductive Tech.
    - Nutrition

- Ottawa General Hospital
  - > 3 500 deliveries / Year
  - **Expertise**
    - Epidemiology
    - Neurodevelopment
    - Health service
    - Artificial Reproductive Tech.

- CHU de Sherbrooke
  - > 2 500 deliveries / Year
  - **Expertise**
    - Genetics / epigenetics
    - Neurodevelopment
    - Cardiovascular disorders
    - Placental disorders
    - Psycho-socio economic
    - Clinical epidemiology
    - WEB-based learning

- RUIS Université de Sherbrooke
  - 10 delivery units
  - > 12 000 deliveries / Year

- RUIS Université Laval
  - 25 delivery units
  - > 16 000 deliveries / Year
  - **Expertise**
    - Genetics
    - Cardiovascular disorders
    - Placental disorders
    - Metabolism / growth
    - Health service
    - Environmental exposures

- CUSM
  - > 3 500 deliveries / Year
  - **Expertise**
    - Epigenetics
    - Neurodevelopment
    - Stress & psycho-sociology
    - Metabolism / growth
    - Assisted reproductive tech.
    - Biostatistics
    - Health service
SCIENTIFIC PARADIGM of IRNPQEO

Determinants
- Genetic
  - Paternal, maternal genes
  - Epigenetic changes
- Environmental
  - Medical maternal status
  - Social, demographic factors
  - Public health network
  - Social vulnerability
  - Lifestyle
  - Environmental chemicals
  - Nutritional status
  - Other Factors (ART)
  - Paternal factors (lifestyle, health)

Pregnancy
- Abnormal early embryogenesis
- Abnormal placentation
- Placenta growth restriction
- Epigenetics changes
- Endothelial dysfunction
- Inflammatory responses
- Oxidative stress...

Delivery & early environment
- Delivery mode
- Adverse conditions
- Perinatal hypoxemia

Early Infancy 0-2 years
- Postnatal factors
  - Postnatal care
  - Breastfeeding
  - Psychosocial factors
  - Family environment

Child development
- Neurodevelopment
- Cardiovascular disease
- Metabolic syndrome
- Growth

Life trajectory

Multiples pregnancies

Postnatal factors

Child development

Life trajectory
Research Programme - Projets

• Projet 1. ART Cohort
• Projet 2. IUGR sub cohort
• Projet 3. Preterm Birth Subcohort
• Projet 4. Birth Defects Subcohort
Methodology

- Creation of a cohort of 3000 femmes enceintes
  - From whence our sub cohorts.
  - That will provide our non-exposed patients

- Création of an ART cohort

- Creation of a cohorte of 1000 cases of congenital anomalies
Structure of IRNPQ

Mission

- Enhance the quality and impact of perinatal research in Quebec;
- Train the next generation of researchers in an environmental integrating the 4 pillars of CIHR;
- Create an innovative provincial model ensuring optimal care and evidence-based public policies

Committee Structure

Clinical Research Pillar
- Clinical Research Platform
- Methodological and Technical Support Group
- Study Data-management platform (MHICC)
- Bio-specimen management platform

Repository Pillar
- Databanks Repository
- Biobank Repository

Meta-platform Pillar
- Ethics
- KT
- Social policy

Collaborating Centres and Partners

Training Pillar
Comités de l’IRNPQ

Scientific Committee

Executive Committee

Managing Director

External Advisory Committee

Research Pillar Committee

Repository Pillar Committees
1. Databank
2. Biobank

Meta-platform Pillar Committees
- Ethics
- KT
- Social policy

Training Pillar Committee
Challenges to MIREC and IRNPQEO

- **Governance Policy**: who ‘owns’ data and who is responsible for biospecimens; ensuring appropriate access to specimens: **NEED STRONG ETHICS**

- **Biobanking**: a complex challenge: start-up cost, space, equipment, technical expertise, maintenance
Lessons learned - Asking the right research questions is the most important

- Set stage (sufficient time, conviviality, key players) for serious and intense debates to identify are the most important scientific questions for the network – this is **the most important step**…

- The research design solutions will follow….
Challenges for MIREC and IRNPQEO

- Ensuring funding for cohort: traditional funding agencies are not set up to ensure longitudinal follow-up of cohorts outside of the traditional funding cycle: 1 year to start up, 2 years to recruit, 3 years to 2 years of age, end of cycle!!!
Strategic Planning – the NICHD’s Model under new Director Dr. Guttmacher

- Extensive Planning Exercize
- Horizon scanning – visioning the most promising scientific opportunities for the next decade.
- Set an ambitious agenda that inspires the research community
- Think grandly and not narrowly.
- Rely on excellence - internal and external – in developing vision.
Priority areas identified for visioning workshops:

- Plasticity
- Reproduction
- Development
- Developmental Origins
- Behaviour
- Pregnancy and Pregnancy Outcomes
- Diagnostics and Therapeutics
- Environment
- Cognition
Cross cutting areas:

- Analytic and measurement tools and methods.
- Animal and computational models
- Bioethics- Bioinformatics
- Bioengineering
- Biotechnology ad bioengineering
- Developmental Lens
- Differences- disparities across populations.
Cross cutting areas

- Epigenetics/meta-genomics
- Functional status
- Global health
- Implementation science, including health economics
- Nutrition
- Prevention/personalized medicine
- Stem cells
- Systems biology
- Training and mentoring
TRENDS

- Research, to be effective, must anticipate changing morbidity and mortality (SARS).
- Greater orientation toward **biological processes rather than disease** (study of precursor states) – **phenotype** will be a ‘**cloud of biological processes**’ (Claude Laberge)
- Need to Take advantage of natural experiments to study Gene-Environment Interactions
- Importance of **behavior** as determinant of reproductive health.
Transdisciplinary approach

- Translational research requires fluency in three languages: clinical medicine, basic science and clinical epidemiology (M. Kramer)
Priorities for Institute Director

- Permanent mechanism for horizon scanning to find convergence of between knowledge generating capacity and public policy needs.
- Developing a strategic plan for getting from A (current) to B (research excellence) by international benchmarks, in 5-7 years.
Priorities for Institute Director (2)

- Build cross-institute initiatives.
- Put in place a local, regional and provincial ‘Strategy for Patient Oriented Research’, in collaboration with other institutes.
Thank you! Merci!