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# Incidence, Characteristics, and Outcomes of Acute Kidney Injury Treated with Dialysis during Pregnancy and the Postpartum Period

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Graduate Program in Epidemiology and Biostatistics  
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## Abstract

Pregnancy-related acute kidney injury (AKI) may be associated with significant morbidity and mortality in young and often otherwise healthy women. We conducted a retrospective cohort study of all consecutive pregnancies between 1997 and 2011 in Ontario and describe the incidence, characteristics, and outcomes of AKI treated with dialysis (AKI-D) during pregnancy or within 12 weeks postpartum. Of 1,918,789 pregnancies, 188 were complicated by AKI-D (incidence proportion: 1 per 10,000, 95% confidence interval 0.8 to 1.1). Eight women died (4.3% versus 0.01% in the general population) and seven (3.9%) survivors remained dialysis-dependent four months after delivery. The presence of AKI-D was associated with several maternal complications as well as low birth weight, small for gestational age, and preterm birth among infants, although there were no stillbirths and fewer than five neonatal deaths in affected pregnancies. In conclusion, AKI-D in pregnancy is rare. Most affected women and their babies have good short-term outcomes.

## Keywords

Administrative data, health outcomes, retrospective cohort study, pregnancy, acute kidney injury, dialysis

## Co-Authorship Statement

The study presented here was conceived, designed, and executed by Ainslie Hildebrand. Dr. Amit Garg was the primary supervisor and was involved in all aspects of this work. Dr. Jessica Sontrop was the secondary supervisor and provided comprehensive feedback.

A version of the manuscript presented in this thesis was published in the Journal of the American Society of Nephrology on December 15, 2015 (citation below). Each co-author critically appraised the manuscript and provided important feedback for manuscript revision. Kuan Liu and Salimah Shariff also contributed to study design and acquisition and analysis of data.

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## Glossary of Terms

Acidosis – increased acidity in the blood or body tissue

Acute tubular necrosis – kidney failure caused by damage to the tubules (in the kidney), often caused by decreased blood flow

Alkalosis – increased alkalinity in the blood or body tissue

Aminoaciduria – excessive excretion of amino acids in the urine

Calyces – a system of ducts in the kidneys that carry urine

Cardiogenic shock – shock resulting from heart failure

Chorioamnionitis – inflammation of the fetal membranes, caused by infection

Creatinine – a muscle breakdown product that is filtered by the kidneys and excreted in the urine

Edema – swelling caused by excess fluid in body tissues

Endomyometritis – inflammation of the endometrium, caused by an infection

Glomerulonephritis – inflammation of the glomerulus (in the kidney), often caused by an immune response

Glomerulus – a cluster of small blood vessels involved in filtering waste products from the blood

Glucosuria – excessive excretion of glucose in the urine

Gravid – pregnant

Hydronephrosis – kidney swelling due to urine outflow obstruction

Hyperfiltration – increased glomerular filtration rate

Hyperkalemia – abnormally high level of potassium in the blood

Hypokalemia – abnormally low level of potassium in the blood

Hyponatremia – abnormally low level of sodium in the blood

Interstitial nephritis – inflammation of the spaces between the tubules (in the kidney), often caused by an immune response

Inulin – a small, inert polysaccharide molecule that is used to measure kidney function

Ischemia – inadequate blood supply to an organ

Lupus nephritis – inflammation of the kidney, caused by systemic lupus erythematosus

Microangiopathic hemolytic anemia – loss of red blood cells through destruction from passage through small, partially occluded, blood vessels

Nulliparous – no history of pregnancy resulting in childbirth

Polyhydramnios – excessive amniotic fluid in the amniotic sac

Preeclampsia – a condition characterized by high blood pressure and proteinuria in pregnancy

Proteinuria – excessive excretion of proteins in the urine

Pyelonephritis – inflammation of the kidney, caused by infection

Renal cortical necrosis – a rare cause of kidney failure caused by decreased blood flow to the kidney

Thrombocytopenia – abnormally low platelets in the blood

Uremia – a clinical syndrome produced by accumulation of toxins due to kidney failure

Vasoconstriction – constriction of blood vessels, which increases blood pressure

Vasodilation – dilatation of blood vessels, which decreases blood pressure

## Chapter 1

### 1 Introduction

#### 1.1 Background and Overview

Pregnancy-related acute kidney injury (AKI) is associated with significant morbidity and mortality in young and often otherwise healthy women.<sup>1,2</sup> Since the 1960s, the incidence of pregnancy-related AKI in developed countries has declined from 1 in 3,000 to approximately 1 in 18,000.<sup>1</sup> This trend has been closely linked to improved obstetrical care and dramatic reductions in first-trimester AKI attributable to septic abortions.<sup>3</sup> However, these trends are less relevant in contemporary populations. The changing risk profile of pregnant North American women includes lower parity, older age, higher body mass index, and greater comorbidities such as hypertension, diabetes mellitus, and chronic kidney disease, as well as increased use of reproductive technologies resulting in multifetal gestations.<sup>4-8</sup> These changes may have a unique impact on the incidence and outcomes of pregnancy-related AKI.

We reviewed the literature to better understand kidney function and AKI in pregnancy, and to identify knowledge gaps for further study. We conducted the present study to determine the incidence, characteristics, and outcomes of the most severe cases of AKI in pregnancy, namely those treated with dialysis, in a contemporary cohort of 1.9 million pregnancies in Ontario, Canada.

## Chapter 2

### 2 Literature Review

#### 2.1 The Normal Kidney

##### 2.1.1 Brief Overview of Kidney Function

The kidney is a vital organ and has several key functions. These include (1) excretion of waste products of metabolism such as urea, creatinine, and uric acid, (2) regulation of fluid and electrolytes, including sodium, potassium, and hydrogen, and (3) secretion of hormones that regulate local and systemic hemodynamics, red cell production, and mineral metabolism.<sup>9</sup>

##### 2.1.2 Measurement of Kidney Function

The glomerular filtration rate is used to assess the level of kidney function and is equal to the sum of the filtration rates in all functioning nephrons (filtration units in the kidney).<sup>9</sup> This can be measured by timing urinary clearance of inulin, a physiologically inert substance that is freely filtered by the glomerulus without being secreted, reabsorbed, synthesized, or metabolized by the kidney.<sup>10</sup> However, this method is complex and even though less cumbersome methods for measuring clearance are available (using alternative filtration markers and plasma clearance), it has largely been replaced by estimations of glomerular filtration rate using creatinine clearance or estimation equations such as the Cockcroft-Gault equation,<sup>11</sup> the Modification of Diet in Renal Disease (MDRD) study equations,<sup>12</sup> and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.<sup>13</sup> All of these equations are dependent on serum creatinine concentration, with higher serum creatinine concentrations translating to lower estimated glomerular filtration rates.

## 2.2 The Kidney in Pregnancy

### 2.2.1 Brief Overview of Physiologic Changes in Pregnancy

Several anatomic and physiologic changes occur in the kidney and urinary tract to accommodate pregnancy. Understanding these changes is essential to accurate recognition and management of AKI during pregnancy and the postpartum period.

Both kidney length and volume change during pregnancy. Kidney volume increases by up to 30% as a result of increases in vascular and interstitial spaces, and kidney length increases by 1-1.5 cm with dilatation of the urinary collecting system.<sup>14</sup> Dilatation of the renal pelvises, calyceal systems, and ureters occurs as early as 6 weeks gestation and is typically more pronounced on the right side.<sup>15</sup> Hydronephrosis occurs in up to 80% of women.<sup>15</sup> Urinary stasis in this setting can also predispose women to ascending urinary tract infections such as pyelonephritis.<sup>15</sup>

Several hemodynamic changes also occur within the maternal circulation that contribute to hyperfiltration, the hallmark of healthy adaptation to pregnancy. These include vasodilation, decreased systemic vascular resistance, and decreased arterial pressure, which nadirs between 18 and 24 weeks gestation.<sup>16</sup> Plasma volume increases by approximately 1 L and total body water increases by 6-8 L (primarily in the extracellular compartment), which can result in edema during pregnancy.<sup>17,18</sup> Cardiac output increases due to decreased afterload in this setting.<sup>16</sup> Coinciding with these changes, renal plasma flow increases by 80% and glomerular filtration rate increases by 40-60% by the second half of pregnancy, clinically manifesting as a decrease in circulating creatinine, urea, and uric acid.<sup>17</sup> Renal plasma flow falls rapidly after 36 weeks gestation, followed by normalization of glomerular filtration rate.<sup>19</sup>

In addition to the effect of hyperfiltration, altered tubular reabsorption is likely also responsible for increased levels of urinary protein,<sup>20</sup> glucose,<sup>21</sup> and amino acids<sup>22</sup> during pregnancy. However, in limited studies designed primarily to determine mechanisms, results are inconclusive and the clinical relevance of glucosuria and aminoaciduria in pregnancy is not known. While the upper limit of normal for proteinuria in pregnancy



cited in obstetrical guidelines is 300 mg/24-hour period, double the upper limit of normal for the non-gravid state, significant proteinuria in pregnancy is not considered adaptive.<sup>23</sup>

Several other physiologic changes occur during pregnancy that result in mild hyponatremia,<sup>24</sup> mild hypokalemia,<sup>25</sup> and chronic respiratory alkalosis.<sup>26</sup> These, and other anatomic and physiologic changes, typically return to pre-pregnancy state within a few weeks postpartum.

## 2.2.2 Measurement of Kidney Function in Pregnancy

Hyperfiltration in pregnancy results in a physiologic decrease in serum creatinine concentration by an average of 35 micromol/L.<sup>17</sup> This renders estimations of glomerular filtration rate based on serum creatinine concentration inaccurate. The Cockcroft-Gault equation has been shown to underestimate glomerular filtration by 25% in 23% of cases studied.<sup>27</sup> The MDRD equation underestimated glomerular filtration by 25% in 61% of cases studied.<sup>27</sup> The CKD-EPI equation, which was developed to provide a more accurate estimate of glomerular filtration among patients with higher glomerular filtration rates,<sup>28</sup> has not been assessed in pregnancy. Measurement of creatinine clearance with a 24-hour urine collection is also imprecise during pregnancy due to the delay between urine formation and collection that results from urinary stasis with dilatation of the lower urinary tract.<sup>29</sup> Considering these limitations, assessment of kidney function in pregnancy is restricted to examining trends in serum creatinine concentration, the interpretation of which is also dependent on the presence of baseline measures of serum creatinine prior to pregnancy.

## 2.3 Acute Kidney Injury

### 2.3.1 Definition of Acute Kidney Injury in the General Population

AKI is a sudden loss of kidney function, resulting in the retention of urea and other waste products, and dysregulation of fluid and electrolytes.<sup>30</sup> This can result from specific diseases of the kidney (e.g., interstitial nephritis, glomerulonephritis) or extrarenal pathology (e.g. dehydration, heart failure, sepsis, obstruction).<sup>30</sup> In severe cases, this manifests as metabolic acidosis, electrolyte abnormalities, fluid retention, hypertension,

and, in some cases, clinical symptoms of uremia such as confusion.<sup>31</sup> Measuring changes in serum creatinine concentration is considered the standard of care for detection of AKI, however historically there has been no consensus on the definition or diagnostic criteria for AKI in any population.<sup>32</sup> Only recently have several consensus definitions for AKI been developed for use in the general population to provide a more standardized quantitative definition of AKI (Table 1). These include the RIFLE (Risk, Injury, Failure; Loss, End-Stage Renal Disease)<sup>30</sup> and Acute Kidney Injury Network (AKIN)<sup>33</sup> criteria, and the Kidney Disease: Improving Global Outcomes (KDIGO) modifications of the AKIN criteria.<sup>34</sup> These criteria take into account the timing and magnitude of changes in serum creatinine and urine output.

**Table 1: Acute kidney injury diagnostic criteria**

Criteria	Serum creatinine criteria			Urine output criteria
	RIFLE <sup>30</sup>	AKIN <sup>33</sup>	KDIGO <sup>34</sup>	
Definition	Increase in serum creatinine of >50% developing over <7 days	Increase in serum creatinine of 0.3 mg/dL (26.5 micromol/L) or >50% developing over <48 hours	Increase in serum creatinine of 0.3 mg/dL (26.5 micromol/L) developing over 48 hours or >50% developing over 7 days	Urine output of <0.5 mL/kg/hour for >6 hours

Adapted from “Criteria for Acute Kidney Injury,” by P. Fatehi and C. Hsu. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA.<sup>35</sup>

However, because of variability in the application of these criteria, the incidence of AKI in the community is still not certain. In a large population-based study from the United States using changes in serum creatinine to define AKI, the overall incidence rate of non-dialysis-requiring AKI was 384.1 per 100,000 person-years and increased from 322.7 to 522.4 per 100,000 person-years from 1996 to 2003.<sup>36</sup>

### 2.3.2 Definition of Acute Kidney Injury in Pregnant Populations

Given the limitations of using serum creatinine-based measures of kidney function in pregnancy (discussed in Section 2.2.2), there are obvious limitations to using the serum creatinine-based diagnostic criteria for AKI highlighted in Table 1 (Section 2.3.1) in pregnancy, despite being widely adopted for use in the general population.<sup>30,33,34</sup> Mild increases in serum creatinine during pregnancy, which may represent marked reductions

in glomerular filtration rate among women with normal or near normal values at baseline, may not be appreciated at the time of presentation using these criteria.<sup>37</sup> Therefore, although a wide range of criteria have been used to define pregnancy-related AKI in previous studies, including RIFLE criteria<sup>38</sup> and hospital diagnosis codes,<sup>2,39,40</sup> these should be expected to underestimate its true incidence. Even in the general population, hospital diagnosis codes for AKI lack sensitivity.<sup>41</sup> At this point, the diagnosis of AKI in pregnancy is primarily a clinical one, dependent on careful interpretation of serum creatinine values in the context of known baseline measures of kidney function by an astute clinician.

### 2.3.3 Role of Dialysis in Acute Kidney Injury

In both non-pregnant and pregnant populations, management of AKI is supportive and is focused on identification and treatment of the underlying cause (which, depending on the cause in pregnancy, may necessitate early delivery of the fetus).<sup>23,42</sup> However, if conservative therapy fails to control complications such as acidosis, hyperkalemia, volume overload, or symptomatic uremia, dialysis may be indicated.<sup>34,42</sup> Dialysis is a process whereby blood is removed from the body and circulated through an extracorporeal fluid circuit, then returned to the patient. Waste products and excess fluid are removed from the blood via diffusion (movement of solute by concentration gradient) and ultrafiltration (movement of fluid and solute by pressure gradient).<sup>43</sup> There are several risks associated with this process, including hypotension, arrhythmia, infection, and bleeding, so clinicians tend to delay initiation of dialysis in cases where they suspect the patient will recover on their own and complications can be managed with medical therapy.<sup>34,43</sup> Although the optimal timing, modality, and dose of dialysis for AKI has not been determined in any population, these clinical indications are universally recognized as indicators of high disease severity and are consistent with the recommendations provided in the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for AKI.<sup>34,42</sup> Literature on maintenance of pregnancy in the setting of end-stage kidney disease suggests that there may be a role for early initiation of intensive hemodialysis to minimize maternal complications and fetal risks from uremia (such as polyhydramnios, preterm birth, premature rupture of membranes, and developmental

delay),<sup>44-46</sup> however there is no evidence that this strategy is being adopted for severe AKI in pregnancy.<sup>42</sup>

## 2.4 Epidemiology of Acute Kidney Injury

### 2.4.1 Epidemiology of Acute Kidney Injury in the General Population

The incidence rate of AKI requiring dialysis in the general population is 24.4 per 100,000 person-years and is increasing by an average of 10% per year.<sup>36,47</sup> In-hospital mortality is approximately 60%.<sup>48-50</sup> Among those who survive, as many as 15% remain on dialysis at the time of discharge.<sup>49,51</sup>

### 2.4.2 Epidemiology of Acute Kidney Injury in Pregnant Populations

The true incidence of AKI in pregnancy is difficult to determine due to the inconsistency of diagnostic criteria used to define AKI and varies considerably across populations depending on demographics and standards of care. However, several general epidemiologic trends can be established from existing studies.

Based on data from several diverse populations since the 1960s, the incidence proportion of AKI in pregnancy has declined dramatically from 1 in 3,000 to 1 in 15,000-20,000 worldwide.<sup>1,52-55</sup> Similarly, the proportion of all AKI cases accounted for by pregnancy-related causes has dropped from 20-40% to 2-10%.<sup>1,53,54</sup> Short-term maternal morbidity after pregnancy-related AKI and dialysis dependence among survivors has also nearly disappeared, previously affecting as many as 30% and 11% of cases respectively. These trends have been closely linked to improved obstetrical care in developed countries and dramatic reductions in first-trimester AKI attributable to fewer septic abortions with the legalization of abortion.<sup>1</sup>

Studies that have examined secular trends of AKI in pregnancy in contemporary North American populations have demonstrated a paradoxical increase in incidence of AKI defined by hospital diagnosis codes (Table 2)<sup>39,40,56</sup> which is in keeping with the trends observed in the general population using serum creatinine-based definitions of AKI.<sup>36,47</sup> Callaghan et al. reported a significant increase in the incidence proportion of AKI in pregnancy in the United States between 1998 and 2008, from 2.3 to 4.5 per 10,000

deliveries ( $P < 0.05$ ).<sup>40</sup> A similar trend was observed in Canada where the incidence proportion of AKI in pregnancy increased from 1.6 to 2.7 per 10,000 deliveries between 2003 and 2010 ( $P < 0.05$ ).<sup>39,56</sup> This temporal increase was restricted to pregnancies complicated by hypertensive disorders and was especially pronounced among women with gestational hypertension and proteinuria (i.e. preeclampsia).<sup>56</sup> These trends also correspond to increases in the rate of deliveries among women with pre-existing medical conditions such as hypertension, diabetes mellitus, and chronic kidney disease (known risk factors for preeclampsia) and those with complications such as preeclampsia and postpartum hemorrhage noted in other population-based studies.<sup>7</sup>

**Table 2: Contemporary population-based studies of acute kidney injury in pregnancy**

Study (Publication Date)	Population (Years)	AKI Definition	Incidence Proportion	Associated Conditions
Liu et al. <sup>39</sup> (2010)	All hospital deliveries in Canada (except Quebec) (2003-2007)	ICD-10 diagnosis codes for AKI (Canadian Institute for Health Information – Discharge abstract database)	1.6 to 2.3 cases/10,000 deliveries from 2003 to 2007	Not reported
		CCI procedure codes for dialysis (Canadian Institute for Health Information – Discharge abstract database)	0.4 to 0.4 cases/10,000 deliveries from 2003 to 2007	Not reported
Callaghan et al. <sup>40</sup> (2012)	All delivery and postpartum hospitalizations in a stratified sample of community hospitals in the United States (1998-2009)	ICD-9 diagnosis codes for AKI	2.3 to 4.5 cases/10,000 deliveries from 1998 to 2009	Not reported
Mehrabadi et al. <sup>56</sup> (2014)	All hospital deliveries in Canada (except Quebec) (2003-2011)	ICD-10 diagnosis codes for AKI (Canadian Institute for Health Information – Discharge abstract database)	1.6 to 2.7 cases/10,000 deliveries from 2003 to 2010	Age >35, nulliparity, multifetal gestation, hypertension, diabetes, preeclampsia, postpartum hemorrhage, sepsis, cardiac failure, caesarean section

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CCI procedure codes for dialysis (Canadian Institute for Health Information – Discharge abstract database)	10.4% to 7.6% of AKI cases from 2003 to 2010	Not reported
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## 2.5 Etiology of Acute Kidney Injury in Pregnancy

Clinical investigation for the cause of AKI in pregnancy is the same as in the non-pregnant population, which includes consideration of pre-renal, renal, and post-renal etiologies.<sup>42</sup> However, there are several conditions known to precipitate AKI that are either unique to pregnancy or worsened by the gravid state. Unfortunately, there are limited data on the incidence, risk factors, and outcomes of these conditions, including the associated risk of AKI. The following three sections elaborate on three main causes of AKI in pregnancy that can occur in the setting of many common medical or surgical complications of pregnancy. However, much of this information is based on known pathophysiologic mechanisms, rather than population-based studies designed to assess the risk of AKI in these settings.

### 2.5.1 Ischemic Injury

Volume depletion from any cause can precipitate AKI in pregnancy through pre-renal ischemia or acute tubular necrosis. Prior to 20 weeks gestation, this may be due to hyperemesis gravidarum, a condition defined by refractory nausea and vomiting accompanied by weight loss in excess of 5% of pre-pregnancy body weight, or obstetrical hemorrhage due to a spontaneous or induced abortion.<sup>42</sup> Later in pregnancy, cardiogenic shock as a result of an amniotic fluid embolism, obstetrical hemorrhage from placental abruption, or postpartum hemorrhage are more common.<sup>42</sup> Sepsis due to chorioamnionitis, endomyometritis, or pyelonephritis can lead to AKI in pregnancy through similar mechanisms.<sup>42,57</sup> Renal cortical necrosis can also occur in these settings, however this is now almost exclusively limited to developing countries where access to prompt obstetrical care is limited.<sup>42,58</sup>

## 2.5.2 Hypertensive Disorders of Pregnancy

Preeclampsia refers to the new onset of hypertension and either proteinuria or end-organ dysfunction after 20 weeks gestation.<sup>23</sup> The frequency of preeclampsia ranges from 2% to 7% in healthy nulliparous women and increases substantially in women with advanced maternal age, multifetal gestation, chronic hypertension, diabetes mellitus, and chronic kidney disease.<sup>59,60</sup> Preeclampsia is the leading cause of maternal morbidity and mortality worldwide and is the most common cause of AKI during pregnancy.<sup>61</sup> Although most women experience only minor transient increases in serum creatinine; when accompanied by features of HELLP syndrome (defined by the presence of hemolysis, low platelet count, and elevated liver enzymes), AKI has been reported in 3-15% of cases.<sup>62,63</sup> In addition to the direct effect of preeclampsia on renal function via endothelial injury, secondary effects of intravascular volume depletion, vasoconstriction, and activation of inflammatory and coagulation cascades in these settings can increase the risk of kidney failure in pregnancy.<sup>63</sup>

## 2.5.3 Thrombotic Microangiopathy

Although much less common, thrombotic microangiopathy is another important cause of AKI in pregnancy; which, like preeclampsia, typically presents after 20 weeks gestation. Thrombotic microangiopathy is a pathological process characterized by microangiopathic hemolytic anemia, thrombocytopenia, and variable signs of organ injury from endothelial damage and thrombosis.<sup>64</sup> Thrombotic microangiopathy is a defining feature of thrombotic thrombocytopenic purpura (TTP), a condition caused by a congenital or acquired deficiency in ADAMTS13 (A Disintegrin And Metalloprotease with a ThromboSpondin type 1 motif, member 13, an enzyme that works to minimize microvascular thrombosis by cleaving complexes formed by von Willebrand factor and platelets).<sup>65</sup> However, thrombotic microangiopathies may be caused by other mechanisms, including enteric infection with Shiga toxin (known as hemolytic uremic syndrome [HUS]), drug-mediated toxicity or immune reaction, and complement dysregulation (known as atypical HUS) or may be the manifestation of several other underlying disorders in up to 60% of cases.<sup>65</sup> Although thrombotic microangiopathy occurs in only 1 in 25,000 pregnancies, pregnancy accounts for 10-25% of cases of

thrombotic microangiopathy and is a known trigger for ADAMTS13 deficiency in TTP and uncontrolled complement activation in atypical HUS.<sup>66-68</sup> AKI is most common among patients with atypical HUS with severe AKI requiring dialysis reported in over 80% of cases.<sup>68</sup>

## 2.6 Outcomes of Acute Kidney Injury in Pregnancy

In a population-based study of hospital deliveries in Canada between 2003 and 2011, the proportion of pregnancies affected by AKI that required dialysis was 8.8% and maternal death occurred in 2.8% of cases.<sup>56</sup> However, based on the information provided, acute dialysis may not have been completely captured in this study,<sup>56</sup> and this data does not reflect dialysis dependence among survivors. Reports of this outcome are limited to two small studies from Brazil and Egypt, in which AKI was defined by treatment with dialysis and RIFLE criteria within admission to the intensive care unit respectively.<sup>38,69</sup> These studies suggest that up to 50% of women may remain dialysis dependent postpartum and maternal death may occur in up to 30% of cases of severe AKI.<sup>38,69</sup> However, these studies represent single-center experiences prone to selection biases. No study to-date has examined the perinatal complications associated with AKI of any severity in a contemporary developed population.



## Chapter 3

### 3 Rationale for Research Approach

#### 3.1 The Need for Research

Several attempts have been made to understand pregnancy-related AKI in contemporary populations.<sup>2,38–40,56,69,70</sup> These studies have been limited by small sample sizes,<sup>38,69</sup> highly selected populations,<sup>38,69,70</sup> and use of definitions for AKI that have not been validated in pregnancy and in some cases might lack clinical relevance.<sup>2,39,40,56</sup> Trends in older maternal age and greater chronic disease among pregnant North American women appear to have a negative impact on the incidence of pregnancy-related AKI in contemporary populations.<sup>7,56</sup> How these trends impact the incidence, characteristics, and outcomes of more severe presentations of AKI, such as those treated with acute dialysis during pregnancy or the postpartum period, remains unclear. Small, single center studies suggest that maternal morbidity and mortality may still be high in these cases, while perinatal complications remain uncertain.<sup>38,69</sup>

#### 3.2 Our Research Approach

In 2013, Ontario had a population of nearly 14 million residents with approximately 140,000 births occurring each year over the previous 5 years (2009–2013).<sup>71,72</sup> All permanent residents of Ontario receive universal access to hospital and physician services from a single provincial payer. Comprehensive health administrative data collected for this purpose is de-identified and housed in a large repository at the Institute for Clinical Evaluative Sciences (ICES) for the purpose of health services research.<sup>73</sup> This data can be leveraged to conduct large population-based studies of health outcomes.

We used Ontario's health administrative data to identify all consecutive pregnancies between 1997 and 2011 and describe the incidence, characteristics, and outcomes of AKI treated with dialysis (AKI-D) during pregnancy or the postpartum period using administrative data from several sectors of health care.

### 3.2.1 Strengths of Ontario's Health Administrative Data

There are several advantages to using this data. Ontario's health administrative databases are large and provide the opportunity to identify populations retrospectively with minimal selection bias and loss to follow-up (only by emigration out of the province, which is less than 0.5% per year), ensuring high generalizability.<sup>74</sup> Access to large population-based cohorts through this strategy also allows researchers to examine rare events such as AKI in pregnancy with high statistical power, low cost, and limited time. Because data from several sectors of health care (vital statistics, physician services, hospital records, medications) can be linked, a wide range of variables can be ascertained. Many of these variables, including those used to study AKI in pregnancy, have proven valid in previous studies.<sup>75-83</sup> In addition, because maternal hospital records can be linked to infant hospital records, there is a unique opportunity to examine perinatal characteristics not addressed in previous studies.

### 3.2.2 Limitations of Ontario's Health Administrative Data

However, administrative data is limited by its primary purpose, which is to guide remuneration and resource allocation. As a result, there are information gaps in history and physical examination variables, laboratory data, and medication use for those under the age of 65.<sup>73</sup> Further, although some administrative data codes have been validated for use in research, the majority have not. Many coding algorithms lack sensitivity and misclassification of variables can occur. This misclassification is typically 'non-differential', as acquisition of data is independent of the research question and not subject to recall bias, and should be expected to bias of the estimate of effect towards the null hypothesis (Type II error) and/or result in suboptimal control of confounding variables.<sup>84</sup> Medical procedures are generally considered more reliable than diagnoses obtained from medical records given the financial incentives and processes in place to submit and encode data.<sup>84</sup>

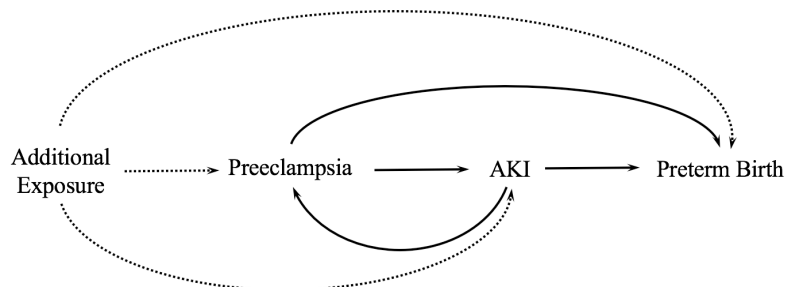
## 3.3 Challenges of Pregnancy Outcomes Analyses

There are several analytic challenges to consider when conducting population-based pregnancy outcome studies. First, administrative data sources in Canada only capture

pregnancies resulting in childbirth (live or stillborn), so pregnancies resulting in a spontaneous or therapeutic abortion prior to 20 weeks gestation (which may occur in up to 25% of pregnancies) are not captured.<sup>85</sup> Second, because women may have several pregnancies during the data accrual period, exposure and outcome data may be clustered by mother if pregnancy is used as the unit of analysis. Failure to account for this intracluster correlation may bias the estimate of effect towards rejecting the null hypothesis (Type I error).<sup>86</sup> However, several modeling approaches may be used to address this.<sup>86,87</sup> Third, because pregnancy is often the first healthcare encounter for women included in these studies, data on preexisting conditions may not have been captured in administrative data. This may result in misclassification of pre-pregnancy conditions as pregnancy-related if identified during prenatal care.

Finally, while there are several conditions known to be associated with AKI in pregnancy,<sup>56</sup> the relationship between pre-pregnancy maternal characteristics, medical complications of pregnancy, and adverse maternal and perinatal outcomes is complex. Many of these variables are highly correlated and there is limited data to support assumptions about the pathophysiologic pathway that represents the relationship between suspected risk factors, confounders, and outcomes, and the directionality of these associations. This makes it difficult to adequately control for confounding and, in some cases, even assign labels such as ‘exposure’ and ‘outcome’. For example, consider the proposed association between preeclampsia, AKI, and preterm birth highlighted in Figure 1 (oversimplified for demonstration purposes).

**Figure 1: Potential causal pathways for the association between preeclampsia, AKI, and preterm birth**



Depending on the causal pathway of interest, AKI may be a ‘mediator’ of the association between preeclampsia and preterm birth, a ‘confounder’ if not actually on the causal pathway between preeclampsia and preterm birth, or an ‘exposure’ relative to preeclampsia or preterm birth. Further, preterm birth could actually precede the clinical diagnosis of preeclampsia and/or AKI if there is another ‘exposure’ (risk factor or characteristic) at play. This other exposure, such as the condition lupus nephritis, may act both as a cause of preterm birth and a risk factor for either preeclampsia, AKI, or both. This would reverse the sequence of identification of events, but would not necessarily mean that preterm birth caused preeclampsia or AKI. For this reason, the purpose of this study was not to establish causality, but rather to determine the direction and magnitude of associations in order to create a framework for physicians to better identify women at risk.

## Chapter 4

### 4 Research Questions and Framework

#### 4.1 Research Questions

##### 4.1.1 Incidence of AKI-D

Among all pregnancies resulting in childbirth over a 15-year period (1997-2011) in Ontario, Canada, what proportion develop acute kidney injury treated with dialysis (AKI-D) during pregnancy or the postpartum period?

*Hypothesis:* We expected that the proportion of pregnancies complicated by AKI-D during pregnancy or the postpartum period in this era would be low and less than the reported incidence proportion of pregnancy-related AKI in previous studies, which ranges from 1.6 to 4.5 cases per 10,000 deliveries.<sup>39,40,56</sup>

##### 4.1.2 Maternal Complications Associated with AKI-D

Among these pregnancies, does the presence (vs. absence) of selected maternal complications associate with a higher incidence of AKI-D in pregnancy or the postpartum period?

We selected maternal complications (listed in Table 3) based on biological plausibility, previous literature supporting an association (when available), and an ability to reliably ascertain with our data sources.

**Table 3: Maternal complications of interest**

Maternal complications during pregnancy or the postpartum period
Multifetal gestation
Hyperemesis gravidarum
Gestational hypertension
Preeclampsia
Thrombotic microangiopathy
Pyelonephritis
Sepsis
Caesarean delivery
Postpartum hemorrhage

*Hypothesis:* We expected that the incidence of AKI-D will be higher among women with record of these complications compared to those without such a record.

#### 4.1.3 Perinatal Complications Associated with AKI-D

Among these pregnancies, does the presence (vs. absence) of AKI-D in pregnancy or the postpartum period associate with a higher incidence of perinatal complications?

We selected perinatal complications (listed in Table 4) based on biological plausibility, previous literature supporting an association (when available), and an ability to reliably ascertain with our data sources.

**Table 4: Perinatal complications of interest**

Perinatal complications
Low birth weight
Small for gestational age
Preterm birth
Stillbirth
Perinatal mortality
Neonatal death

*Hypothesis:* We expected that the incidence of these perinatal complications will be higher among women with AKI-D compared to those without AKI-D.

#### 4.1.4 Maternal Outcomes of AKI-D

Among these pregnancies, does the presence (vs. absence) of AKI-D associate with a higher risk of maternal death within 90 days postpartum? Among survivors of AKI-D, what proportion remain dependent on dialysis between 90 and 120 days postpartum?

*Hypothesis:* We expected that the relative risk of maternal death would be higher among pregnancies complicated by AKI-D compared to those without AKI-D. However, we expected that absolute risk of death in both groups and the risk difference between the two groups would be low. We expected a low proportion of survivors to remain dialysis dependent beyond 90 days postpartum.

## 4.2 Research Framework

In order to address these questions, we conducted a retrospective population-based cohort study of all consecutive pregnancies resulting in childbirth over a 15-year period (1997-2011) in Ontario, Canada to identify incident cases of AKI-D during pregnancy or the postpartum period, determine the concurrent maternal complications that may be associated with AKI-D, and examine perinatal complications and maternal outcomes in relation to AKI-D.

## Chapter 5

### 5 Methods

#### 5.1 Design and Setting

We conducted a retrospective population-based cohort study using linked healthcare databases in Ontario, Canada to study the incidence, characteristics, and outcomes of AKI-D in pregnancy and the postpartum period. Study conduct and reporting follow guidelines (STROBE) for observational studies (Appendix A).<sup>88</sup>

#### 5.2 Ethics

A research ethics board at Sunnybrook Health Sciences Centre in Toronto approved the pre-specified protocol (Appendix B and C). However, numbers of participants were suppressed in the case of five or fewer participants (reported as  $\leq 5$ ) to comply with privacy regulations for minimizing the chance of identification of a study participant.

#### 5.3 Data Sources

##### 5.3.1 Databases

We identified our pregnant population by childbirth and ascertained maternal and perinatal characteristics and outcome data from records in seven linked databases from the Institute of Clinical Evaluative Sciences (ICES). Vital statistics and location of residence were obtained from the Registered Persons Database, which contains demographic information for all Ontario residents ever issued a health card.<sup>73</sup> We used inpatient and outpatient diagnostic and procedural information to define maternal characteristics and outcome data. The Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) collects demographic, diagnostic, and procedural variables for all acute care, chronic, and day surgery admissions.<sup>73</sup> The Ontario Health Insurance Plan (OHIP) database contains fee-for-service claims for inpatient and outpatient physician services.<sup>73</sup> Each claim record includes information about the physician, service provided, and diagnostic information. Diabetic and hypertensive patients were identified using the Ontario Diabetes Database and the



Ontario Hypertension Database. These databases are derived by ICES and use a validated algorithm to identify diabetic and hypertensive patients based on data from CIHI-DAD and OHIP.<sup>76,77</sup> Childbirths and perinatal characteristics were identified using the MOMBABY dataset. This is also an ICES-derived dataset that links the CIHI-DAD inpatient admission records of delivering mothers and their newborns.<sup>73</sup> Maternal cause of death was determined from the Ontario Registrar General Death database, which contains information on all deaths registered in Ontario.<sup>73</sup> Members of our research team have used these databases in previous studies to research health outcomes and health services including those related to AKI-D.<sup>89-92</sup> Ascertainment of variables from these databases were complete, with minor exceptions detailed in Table 5.

**Table 5: Missing data for cohort of 1,918,789 pregnancies resulting in childbirth, 1997 to 2011**

Database	Dates Available	Dates Required	Dates Missing	Data Affected
OHIP	July 1991 to March 2012	April 1991 to March 2012	April 1991 to June 1991	Incomplete capture of pre-pregnancy chronic kidney disease in the 5-years prior to pregnancy for childbirths between January 1997 and March 1997.
ORGD	January 1990 to December 2009	January 1997 to March 2012	January 2010 to March 2012	Missing cause of death for childbirths resulting in maternal death between January 2010 and March 2012.
RPDB	April 1990 to March 2012 (Incomplete)	January 1997 to March 2012	January 1997 to March 2012 (Selected Data)	Missing income quintile in 9851 (0.51%) childbirths and rural residence in 2488 (0.13%) childbirths between January 1997 and March 2012.

Abbreviations: OHIP, Ontario Health Insurance Plan using fee and diagnostic codes; RPDB, Registered Persons Database; ORGD, Ontario Registrar General Death database.

### 5.3.2 Codes

In Ontario, hospital admissions were coded using the International Classification of Diseases, Ninth Revision (ICD-9) (including Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures [CCP]) prior to April 2002 and the International Classification of Diseases, Tenth Revision (ICD-10) (including Classification of Health

Interventions [CCI]) thereafter. Billing claims are submitted using fee and diagnosis codes outlined in the OHIP Schedule of Benefits. Detailed information on coding definitions is provided in Table 6.

**Table 6: Healthcare database codes used for definition of exclusion criteria, exposure and outcome measurements, and maternal and perinatal characteristics**

Variable *	Source	Codes
<b>Exclusion Criteria</b>		
Chronic dialysis	CIHI-DAD OHIP	<b>ICD-9:</b> V451, V560, V568, 36104 <b>ICD-10:</b> T824, Y602, Y612, Y622, Y841, Z49, Z992, N180, E1022, E1023, E1122, E1123, E1322, E1323, E1422, E1423, V560, V568, 36104 <b>CCP:</b> 5127, 5142, 5143 <b>CCI:</b> 1OT53DATS, 1OT53HATS, 1OT53LATS, 1SY55LAFT, 7SC59QD, 1KY76 <b>OHIP:</b> R850, G324, G336, G327, G862, G865, G099, R825, R826, R827, R833, R840, R841, R843, R848, R851, Z450, Z451, Z452, G864, R852, R853, R854, R885, G333, H540, H740
Kidney transplantation	CIHI-DAD OHIP	<b>ICD-9:</b> V420, 99681 <b>ICD-10:</b> T861, N165, Z940 <b>CCP:</b> 6743, 675 <b>CCI:</b> 1PC85 <b>OHIP:</b> E762, S435, E769, S434, E771, Z631, G347, G348, G412, G408, G409
<b>Outcomes</b>		
Acute kidney injury treated with dialysis	CIHI-DAD OHIP	<u>Hemodialysis</u> <b>CCI:</b> 1PZ21HQBR <b>CCP:</b> 5195, 6698 <b>OHIP:</b> R849, G323, G325, G866 <u>Continuous veno-venous hemodialysis</u> <b>CCI:</b> 1PZ21HQBS <b>OHIP:</b> G082, G083, G085, G090, G091, G092, G093, G095, G294, G295 <u>Peritoneal dialysis</u> <b>CCI:</b> 1PZ21HPD4 <b>OHIP:</b> G330, G331
Chronic dialysis	OHIP	<b>OHIP:</b> R849, G323, G325, G326, G860, G863, G866, G330, G331, G332, G861, G082, G083, G085, G090, G091, G092, G093, G094, G095, G096, G294, G295 [At least 2 codes on separate days]
Mortality	RPDB ORGD	N/A

<b>Maternal Characteristics Prior to Pregnancy<sup>†</sup></b>		
Age	RPDB	N/A
Neighborhood income	RPDB	N/A
Rural residence	RPDB	N/A
Previous pregnancy <sup>‡</sup>	MOMBABY	<b>MOMBABY:</b> [B_BDATE] in the infant CIHI-DAD record
Hypertension	OHD <sup>§</sup>	N/A
Diabetes mellitus	ODD <sup>  </sup>	N/A
Chronic kidney disease	CIHI-DAD OHIP	<b>ICD-9:</b> 4030, 4031, 4039, 4040, 4041, 4049, 582, 583, 580, 581, 584, 585, 586, 587, 5880, 5888, 5889, 5937 <b>ICD-10:</b> E102, E112, E132, E142, I12, I13, N08, N18, N19 <b>OHIP:</b> 403, 585
General practitioner /Family physician	IPDB	N/A
Internal medicine specialist	IPDB	N/A
Nephrologist <sup>¶</sup>	OHIP	<b>OHIP:</b> C132, C101, C138, G860, G323, E083, C137, C135, A135
<b>Maternal Complications During Pregnancy or the Postpartum Period<sup>**</sup></b>		
Multifetal gestation	MOMBABY	<b>MOMBABY:</b> [B_MULTIPLE BIRTH] or [M_MULTIPLE BIRTH] in the infant/maternal CIHI-DAD record
Hyperemesis gravidarum	CIHI-DAD OHIP	<b>ICD-9:</b> 64300, 64301 <b>ICD-10:</b> O21001, O21003, O21009, O21101, O21103, O21109 <b>OHIP:</b> 643
Gestational hypertension	CIHI-DAD	<b>ICD-9:</b> 64290, 64291, 64292, 64293, 64294 <b>ICD-10:</b> O13
Preeclampsia (includes eclampsia)	CIHI-DAD OHIP	<b>ICD-9:</b> 64240, 64241, 64242, 64243, 64244, 64250, 64251, 64252, 64253, 64254, 64260, 64261, 64262, 64263, 64264, 64270, 64271, 64272, 64273, 64274 <b>ICD-10:</b> O14, O15 <b>OHIP:</b> 642
Thrombotic microangiopathy <sup>††</sup>	CIHI-DAD OHIP	<b>ICD-9:</b> 4466 <b>ICD-10:</b> M311 <b>OHIP:</b> 287
Plasma exchange <sup>††</sup>	OHIP	<b>OHIP:</b> G272, G277, G278, G290
Pyelonephritis	CIHI-DAD OHIP	<b>ICD-9:</b> 59000, 59001, 59010, 59011, 5902, 59080, 59081, 5909 <b>ICD-10:</b> N110, N111, N151, O23001, O23002, O23003, O23004, O23009 <b>OHIP:</b> 590

Sepsis	CIHI-DAD OHIP	<b>ICD-9:</b> 0031, 0380, 0381, 0382, 0383, 03840, 03841, 03842, 03843, 03844, 03849, 0388, 0389, 0545, 65930, 65931, 65933 <b>ICD-10:</b> A400, A401, A402, A403, A408, A409, A410, A411, A412, A413, A414, A4150, A4151, A4152, A4158, A4159, A4180, A4188, A419, R572, O85002, O85004, O85009 <b>OHIP:</b> 038
Caesarean delivery	CIHI-DAD	<b>ICD-9:</b> 66970, 66971 <b>ICD-10:</b> P034 <b>CCP:</b> 860, 861, 862 <b>CCI:</b> 5MD60AA, 5MD60CB, 5MD60CC, 5MD60CD, 5MD60CE, 5MD60CF, 5MD60CG, 5MD60JW, 5MD60JX, 5MD60JY, 5MD60JZ, 5MD60KA, 5MD60KB, 5MD60KC, 5MD60KD, 5MD60KE, 5MD60KF, 5MD60KG, 5MD60KT, 5MD60RA, 5MD60RB, 5MD60RC, 5MD60RD, 5MD60RE, 5MD60RF, 5MD60RG, 5MD60RH
Postpartum hemorrhage	CIHI-DAD OHIP	<b>ICD-9:</b> 66600, 66602, 66604, 66610, 66612, 66614, 66620, 66622, 66624 <b>ICD-10:</b> O72 <b>OHIP:</b> 666

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#### Perinatal Complications

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Low birth weight	MOMBABY	<b>MOMBABY:</b> [WEIGHT] < 2500g in infant CIHI-DAD record
Small for gestational age (includes intrauterine growth restriction)	CIHI-DAD	<b>ICD-9:</b> 65650, 65651, 65653, 76400, 76401, 76402, 76403, 76404, 76405, 76406, 76407, 76408, 76409, 76410, 76411, 76412, 76413, 76414, 76415, 76416, 76417, 76418, 76419, 76490, 76491, 76492, 76493, 76494, 76495, 76496, 76497, 76498, 76499 <b>ICD-10:</b> P0590, P0591, P0599
Preterm birth	MOMBABY	<b>MOMBABY:</b> [B_GESTWKS_DEL] or [M_GESTWKS_DEL] < 37 weeks in infant/maternal CIHI-DAD record <b>ICD-9:</b> 76500, 76501, 76502, 76503, 76504, 76505, 76506, 76507, 76508, 76509, 76510, 76511, 76512, 76513, 76514, 76515, 76516, 76517, 76518, 76519 <b>ICD-10:</b> P070, P071, P072, P073 <b>OHIP:</b> 765 [ICD-9 and ICD-10 codes were used to define preterm birth when infant data from MOMBABY dataset was missing]
Stillbirth	MOMBABY	<b>MOMBABY:</b> [B_STILLBIRTH] or [M_STILLBIRTH] in infant/maternal CIHI-DAD record
Perinatal mortality	MOMBABY	<b>MOMBABY:</b> [DTHDATE] within 7 days of birth in infant RPDB record or [B_STILLBIRTH] or [M_STILLBIRTH] in infant/maternal CIHI-DAD record
Neonatal death	MOMBABY	<b>MOMBABY:</b> [DTHDATE] within 28 days of birth in infant RPDB record

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Abbreviations: CIHI-DAD, Canadian Institute for Health Information Discharge Abstract Database using International Classification of Disease, Ninth Revision (ICD-9) and Tenth Revision (ICD-10), Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures (CCP), and Classification of Health Interventions (CCI) codes; OHIP, Ontario Health Insurance Plan using fee and diagnostic codes; RPDB, Registered Persons Database; OHD, Ontario Hypertension Database; ODD, Ontario Diabetes Database; N/A, Not applicable.

- \* Variables are defined by the presence of at least one of the listed codes unless otherwise specified.
- † Information on preexisting medical conditions and consultations was ascertained from administrative database codes in the five years prior to pregnancy. Age, neighborhood income, and rural residence were ascertained at time of delivery.
- ‡ Information on previous pregnancies was available since 1991 and included all pregnancies in Ontario resulting in live birth or stillbirth after 20 weeks gestation.
- § The Ontario Hypertension Database is an ICES-derived database that contains all Ontario hypertension patients defined by a) one hospital admission with a hypertension diagnosis, or b) an OHIP claim with a hypertension diagnosis followed within two years by either an OHIP claim or a hospital admission with a hypertension diagnosis.<sup>76</sup>
- || The Ontario Diabetes Database is an ICES-derived database that contains all Ontario diabetes patients defined by the presence of at least one hospital admission with a diabetes diagnosis or an OHIP claim with a diabetes diagnosis.<sup>77</sup>
- ¶ Restricted to physicians who also billed at least 50 dialysis codes (one per day) within one year of consultation service date.
- \*\* Information on medical complications of pregnancy were ascertained from administrative database codes during pregnancy and the postpartum period.
- †† The variable ‘thrombotic microangiopathy treated with plasma exchange’ was defined by receipt of plasma exchange that falls within an admission for thrombotic microangiopathy (using CIHI-DAD codes) or within seven days of a diagnosis of thrombotic microangiopathy (using OHIP codes).

### 5.3.3 Validity

Whenever possible, we defined maternal characteristics, medical complications of pregnancy, and maternal and perinatal outcomes using database codes that have been proven feasible and reliable in prior studies. Operating characteristics for the codes used to define variables where validity studies exist are shown in Table 7. ICD-10 implementation in 2002 did not significantly alter coding practices for common comorbid conditions used in risk assessment in Ontario.<sup>93,94</sup>

**Table 7: Operating characteristics of codes used to define variables where validity studies exist.**

Outcome	Codes Used in Study	Codes Used in Validation	Gold Standard	Operating Characteristics		
				Sn (%)	Sp (%)	PPV (%)
Preterm birth	P070 P071 P072 P073	P070 P071 P072 P073	Identification of preterm delivery as ascertained through chart review by trained personnel. <sup>75</sup>	91.2	98.8	...
Caesarean delivery	P034	P034	Identification of caesarean delivery as ascertained through chart review by	99.8	98.7	...

trained personnel. <sup>75</sup>						
Gestational hypertension	O13	O13	Identification of gestational hypertension as ascertained through chart review by experienced clinicians. <sup>79,80</sup>	10.0-68.2	99.6-99.8	...
Preeclampsia	64240	6424	Identification of 'mild or unspecified preeclampsia' on chart review by obstetricians using criteria established by the American College of Obstetrics and Gynecology. <sup>81</sup>	78.4	64.3	45.3
	64241					
	64242					
	64243					
	64244					
	64250	6425	Identification of 'severe preeclampsia' on chart review by obstetricians using criteria established by the American College of Obstetrics and Gynecology. <sup>81</sup>	66.7	85.0	84.8
	64251					
	64252					
	64253					
	64254					
	64260	6426	Identification of 'eclampsia' on chart review by obstetricians using criteria established by the American College of Obstetrics and Gynecology. <sup>81</sup>	83.3	94.6	41.7
	64261					
	64262					
	64263					
64264	6425	Identification of 'severe preeclampsia and eclampsia' on chart review by obstetrician. <sup>82</sup>	100.0	100.0	100.0	
64270	6426					
64271						
64272	6425		Identification of 'preeclampsia' on chart review by experienced accredited record technicians or certified coding specialists. <sup>83</sup>	76.0	...	94.0
64273	6427					
64274						
	O14	O14	Identification of 'preeclampsia' on chart review using a well-described and accepted definition. <sup>80</sup>	69.3	99.3	74.4
	O15	O15				
Placental Abruption	64120	64120	Identification of placental abruption as ascertained through chart review by experienced accredited record technicians or certified coding specialists. <sup>83</sup>	89.0	...	89.0
	64121	64121				
	64123	64123				
Postpartum hemorrhage	O72	O72	Identification of postpartum hemorrhage as ascertained through chart review by trained personnel. <sup>75</sup>	90.2	98.2	...
Chronic kidney disease	*	*	*	...	...	...

Abbreviations: Sn, Sensitivity (indicates the percentage of women with the condition who are correctly identified as having the condition); Sp, Specificity (indicates the percentage of healthy women who are correctly identified as not having the condition); PPV, Positive predictive value (indicates the percentage of women whose diagnosis is recorded correctly). Ellipses indicate data not reported.

\* Chronic kidney disease was defined using an algorithm of hospital diagnosis codes validated for older adults in the study region.<sup>78</sup> This algorithm identified patients with a median estimated glomerular filtration rate of 38 mL/min/1.73 m<sup>2</sup> (interquartile range, 27 to 52 mL/min per 1.73 m<sup>2</sup>), whereas its absence identified patients with a median estimated glomerular filtration rate of 69 mL/min/1.73 m<sup>2</sup> (interquartile range, 56 to 82 mL/min per 1.73 m<sup>2</sup>).<sup>78</sup>

These coding algorithms were validated against a gold standard from chart review, which in many cases, was performed by a clinician using a well-described and accepted definition of the condition. These coding algorithms have high specificity and high positive predictive value. Sensitivity appears greatest for coding algorithms used to identify more severe disease. However, the operating characteristics reported in Table 7 apply only to the coding algorithm specified and do not necessarily reflect the entire collection of codes used to define characteristics and outcomes in our study. Therefore, these statistics should only be used as a reference source from which the actual operating characteristics of coding algorithms used in this study can be approximated. Our rationale for including codes not previously validated was to improve sensitivity for capture of that variable.

## 5.4 Population

Ontario provides universal access to hospital and physician services for all permanent residents, with about 140,000 births per year over the previous 5 years (2009-2013).<sup>71</sup> We established a cohort of all pregnancies resulting in childbirth between January 1, 1997, and December 31, 2011. Our data sources capture all hospital childbirths in the province, defined as delivery of an infant at a gestational age of  $\geq 20$  weeks.<sup>95,96</sup>

We applied several data cleaning steps to ensure that (1) both maternal and perinatal data could be ascertained for each pregnancy, (2) all pregnancies were among live women of childbearing age, and (3) multiple gestations were not counted as more than one pregnancy.

We assigned an index date to each pregnancy that was 42 weeks prior to delivery. This was used to define the onset of pregnancy and served as a reference point from which a lookback window for assessment of maternal and perinatal characteristics and an outcome assessment window could be defined. We used 42 weeks prior to delivery, the longest term gestational duration, for this purpose to avoid misclassification of conditions identified early in pregnancy as pre-pregnancy conditions. When relevant, the index date marked the onset of the first trimester, the index date plus 12 weeks (and 1 day) marked the onset of the second trimester, and the index date plus 27 weeks (and 1 day) marked

the onset of the third trimester. The postpartum period was defined by the 12 weeks after the delivery date.

We then excluded pregnancies among mothers with a history of end-stage kidney disease (defined as chronic dialysis treatment or kidney transplantation) within 5 years prior to the index date as these women would already have experienced one of the maternal outcomes of interest prior to pregnancy.

## 5.5 AKI-D

We defined AKI-D as receipt of at least one acute dialysis treatment during pregnancy or within 12 weeks postpartum.

## 5.6 Maternal Characteristics

### 5.6.1 Maternal Characteristics Prior to Pregnancy

We collected information on the following maternal characteristics at the time of delivery, assuming that this data would approximate status at the estimated beginning of pregnancy: age, neighborhood income quintile, and location of residence. We collected information on the following characteristics prior to pregnancy using a fixed lookback window of 5 years prior to the index date: number of previous pregnancies, time since previous pregnancy, presence of preexisting hypertension, diabetes mellitus, and chronic kidney disease, and previous physician visits with a general practitioner or family physician, internal medicine specialist, and nephrologist. This lookback window was fixed to avoid information bias based on cohort entry date.

### 5.6.2 Maternal Complications During Pregnancy or the Postpartum Period

We collected information on medical complications during pregnancy or within 12 weeks postpartum (complications such as preeclampsia may occur up to 12 weeks postpartum).<sup>97</sup> These included multifetal gestation, hyperemesis gravidarum, gestational hypertension, preeclampsia, thrombotic microangiopathy, pyelonephritis, sepsis, caesarean delivery, and postpartum hemorrhage.



## 5.7 Perinatal Complications

We collected data on the following perinatal complications at the time of delivery and up to (and including) 28 days after delivery: low birth weight (< 2500 g irrespective of gestational age), small for gestational age (birth weight < 10th percentile for gestational age), preterm birth (birth of a live infant before 37 weeks gestation), stillbirth (fetal death after 22 weeks gestation), perinatal mortality (stillbirth or death of a live-born infant within 7 days) and neonatal death (death of a live-born infant within 28 days).<sup>98–101</sup>

## 5.8 Maternal Outcomes

Maternal outcomes included (1) maternal death on or before 90 days after the date of delivery, and (2) chronic dialysis dependence, defined as the receipt of two or more chronic dialysis treatments between 90 and 120 days (17 weeks) after the date of delivery among survivors of AKI-D.

## 5.9 Statistical analyses

Pregnancy was the unit of analysis in this study. In order to evaluate the extent of within-mother clustering, we first quantified the number of pregnancies resulting in childbirth during our accrual period and the number of unique mothers.

We then determined the proportion of pregnancies affected by AKI-D during the accrual period (also referred to as the incidence proportion) and described the maternal characteristics prior to delivery in relation to AKI-D status. We used standardized differences to compare maternal characteristics in pregnancies with and without AKI-D. Standardized differences are less sensitive to sample size than traditional hypothesis tests and are not affected by clustering. They provide a measure of the difference between groups divided by the pooled standard deviation; a value of  $\geq 0.10$  (10%) is interpreted as a meaningful difference between groups.<sup>102</sup>

We examined the association between maternal complications during pregnancy or the postpartum period and the incidence of AKI-D using generalized estimating equations

and log-binomial models to estimate the relative difference in the proportion of pregnancies affected by AKI-D among those with maternal complications compared to those without maternal complications, and reported the unadjusted incidence proportion ratios and 95% confidence intervals.

We examined the association between AKI-D during pregnancy or the postpartum period and the incidence of perinatal complications similarly using generalized estimating equations and log-binomial models to estimate the relative difference in the proportion of pregnancies resulting in perinatal complications among those with AKI-D compared to those without AKI-D, and again reported the unadjusted incidence proportion ratios and 95% confidence intervals.

We then used generalized estimating equations and log-binomial models to estimate the relative difference in the risk of maternal death among those with AKI-D compared to those without AKI-D. We reported the proportion of pregnancies resulting in maternal death among those with and without AKI-D, the absolute risk difference, unadjusted relative risk with the 95% confidence interval, and the P value for the difference in unadjusted relative risk. We set the level of significance at  $P < 0.05$ .

All analyses were unadjusted due to the small sample size in the AKI-D group, limited data to support assumptions about independence of maternal characteristics from the causal pathway between complications and maternal outcomes, and lack of sensitivity of our data sources for capture of these variables. We used log-binomial models to reflect the binomial distribution of outcomes with a log-link function to estimate incidence proportion ratios and relative risks.<sup>103</sup> Generalized estimating equations were used to account for within-mother clustering from additional pregnancies during follow-up. This model assumes that clusters are independent and that the correlation matrix that represents the within-subject dependencies is estimated as part of the model (which in this case, assumes that the correlation is the same for all pregnancies that share the same mother, regardless of birth sequence).<sup>104</sup> This model is ideal for analyses of many small clusters and is robust even if the working correlation structure is misspecified.<sup>87</sup>

All analyses were conducted using SAS, version 9.3 (SAS Institute Inc., Cary, NC).

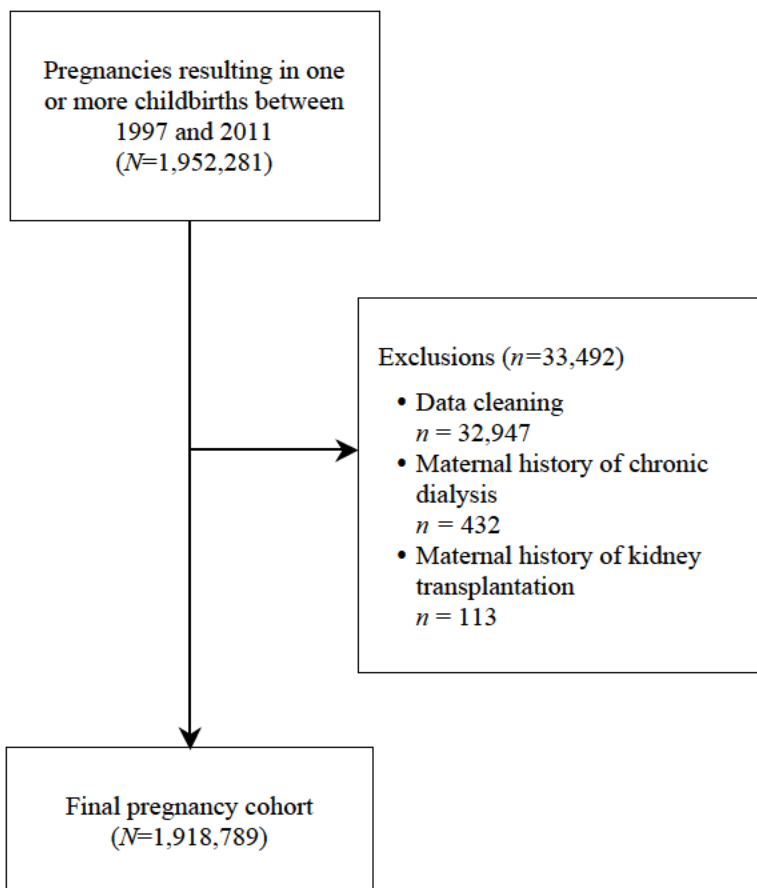
## Chapter 6

### 6 Results

#### 6.1 Pregnancies in Ontario, Canada

There were 1,918,789 deliveries among 1,204,705 unique mothers over the 15-year study period in Ontario, Canada (Figure 2). The median number of pregnancies per mother during the study period was 1 (interquartile range [IQR] 1-2; range 1-11).

**Figure 2: Selection of pregnancy cohort, 1997 to 2011**



#### 6.2 Incidence of AKI-D

Of 1,918,789 pregnancies over the 15-year period, 188 were complicated by AKI-D, representing an incidence proportion of 1 per 10,000 (95% confidence interval, 0.8 to

1.1). These events occurred in 188 different women. Maternal characteristics among pregnancies with and without AKI-D are reported in Table 8.

**Table 8: Maternal characteristics prior to pregnancy among women with and without AKI-D**

Characteristic	AKI-D <i>n</i> =188	No AKI-D <i>n</i> =1,918,601	Standardized Difference *
Unique mothers, <i>n</i>	188	1,204,609	
Age (yrs), median (IQR)	32 (25–35)	30 (26–34)	0.19
Age category (yrs), <i>n</i> (%)			
< 20	11 (5.9)	78,037 (4.1)	0.08
20-29	61 (32.4)	823,665 (42.9)	0.22
30-39	106 (56.4)	956,009 (49.8)	0.13
≥ 40	10 (5.3)	60,890 (3.2)	0.11
Neighborhood income, <i>n</i> (%)			
Lower (quintiles 1 – 2)	95 (50.5)	818,899 (42.7)	0.16
Middle (quintile 3)	26 (13.8)	385,375 (20.1)	0.17
Higher (quintile 4 – 5)	66 (35.1)	704,477 (36.7)	0.03
Rural residence, <i>n</i> (%)	18 (9.6)	202,373 (10.5)	0.03
Number of previous pregnancies, <i>n</i> (%)			
0	104 (55.3)	990,884 (51.6)	0.07
1	57 (30.3)	659,676 (34.4)	0.09
≥ 2	27 (14.4)	268,041 (14.0)	0.01
Time since previous pregnancy (yrs), median (IQR)	0 (0–3)	0 (0–3)	0.05
Recorded preexisting medical conditions, <i>n</i> (%)			
Hypertension	10 (5.3)	25,439 (1.3)	0.22
Diabetes mellitus	≤ 5 (≤ 2.7) †	14,935 (0.8)	0.15
Chronic kidney disease	8 (4.3)	4,568 (0.2)	0.27
Pre-pregnancy physician consultation, <i>n</i> (%)			
General practitioner/family physician	178 (94.7)	1,814,275 (94.6)	0.01
Internal medicine specialist	40 (21.3)	301,323 (15.7)	0.14
Nephrologist	11 (5.9)	9,080 (0.5)	0.31

\* Standardized differences provide a measure of the difference between groups divided by the pooled standard deviation; a value of ≥ 0.10 (10%) is interpreted as a meaningful difference between groups.<sup>102</sup>

† To comply with privacy regulations for minimizing the chance of identification of a study participant, numbers of participants are suppressed in the case of 5 or fewer participants (reported as ≤5), however data was analyzed based on a value of 5 for the purpose of reporting an approximate standardized difference. This may have resulted in overestimation of the standardized difference for the affected variable, ‘diabetes mellitus’.

Pregnancies affected by AKI-D differed significantly from those without AKI-D on several pre-pregnancy characteristics, including age, income quintile, recorded preexisting medical conditions, and specialist consultation.

Among pregnancies complicated with AKI-D, the median maternal age was 32 years (IQR 25-35). The majority of these pregnancies occurred among women living in an urban setting (90.4%) and approximately half (50.5%) of women were in a lower neighborhood income quintile. Most women with AKI-D (94.7%) had been seen by a

general practitioner or family physician prior to pregnancy with 40 (21.3%) having seen an internal medicine specialist and 11 (5.9%) having seen a nephrologist. However, few had recorded preexisting medical conditions; 10 (5.3%) had hypertension, 8 (4.3%) had chronic kidney disease, and 5 or fewer ( $\leq 2.7\%$ ) had diabetes mellitus.

### 6.3 Maternal Complications Associated with AKI-D

The proportion of pregnancies affected by AKI-D in relation to maternal complications during pregnancy or the postpartum period are reported in Table 9. The incidence proportion ratio (IPR) indicates the relative difference in the proportion of pregnancies affected by AKI-D among those with maternal complications compared to those without maternal complications.

**Table 9: Incidence of AKI-D in relation to maternal complications during pregnancy or the postpartum period**

Maternal Complication	Number of AKI-D events / Number at risk	Incidence proportion (per 10,000 pregnancies)	Incidence proportion ratio * (95% confidence interval)
Multifetal gestation	$\leq 5 / 31,260$ †	1.60	0.98 (0.31 to 3.06)
Hyperemesis gravidarum	11 / 77,118	1.43	1.48 (0.81 to 2.73)
Gestational hypertension	6 / 34,625	1.73	1.79 (0.80 to 4.05)
Preeclampsia	40 / 99,726	4.01	4.93 (3.48 to 6.99)
Thrombotic microangiopathy ‡	25 / 8,168	30.61	35.88 (23.56 to 54.62)
Pyelonephritis	6 / 13,511	4.44	4.65 (2.06 to 10.48)
Sepsis	34 / 6,286	54.09	67.17 (46.37 to 97.31)
Caesarean delivery	81 / 488,901	1.66	2.21 (1.66 to 2.95)
Postpartum hemorrhage	33 / 63,177	5.22	6.25 (4.30 to 9.10)

\* All incidence proportion ratios are unadjusted, estimated from log-binomial models using generalized estimating equations to account for within-mother clustering from additional pregnancies during follow-up. The reference category for each row is the absence of the maternal complication.

† To comply with privacy regulations for minimizing the chance of identification of a study participant, numbers of participants are suppressed in the case of 5 or fewer participants (reported as  $\leq 5$ ), however data was analyzed based on a value of 5 for the purpose of reporting an approximate incidence proportion and incidence proportion ratio for AKI-D. Incidence proportions and incidence proportion ratios may be overestimated in these groups.

‡ Thrombotic microangiopathy includes HELLP syndrome. Eight of the 25 patients with thrombotic microangiopathy affected by AKI-D were also treated with plasma exchange.

AKI-D was more likely to occur in pregnancies complicated by preeclampsia, thrombotic microangiopathy, pyelonephritis, sepsis, caesarean delivery, and postpartum hemorrhage, compared to those without such complications. Complications with the strongest associations with the incidence of AKI-D were thrombotic microangiopathy (IPR 35.88, 95% CI 23.56 to 54.62) and sepsis (IPR 67.17, 95% CI 46.37 to 97.31). There was no

association between the incidence of AKI-D and the presence of multifetal gestation, hyperemesis gravidarum, and gestational hypertension.

## 6.4 Perinatal Complications Associated with AKI-D

The incidence of perinatal complications among pregnancies with and without AKI-D is reported in Table 10. The incidence proportion ratio (IPR) indicates the relative difference in the proportion of pregnancies resulting in perinatal complications among those with AKI-D compared to those without AKI-D during pregnancy or the postpartum period.

**Table 10: Incidence of perinatal complications among pregnancies with and without AKI-D**

Perinatal Complication, <i>n</i> (%)	AKI-D <i>n</i> =188	No AKI-D <i>n</i> =1,918,601	Incidence proportion ratio* (95% confidence interval)
Low birth weight	50 (26.6)	102,958 (5.4)	4.66 (3.64 to 5.96)
Small for gestational age	15 (8.0)	46,080 (2.4)	3.16 (1.90 to 5.27)
Preterm birth	61 (32.4)	242,844 (12.7)	2.49 (2.06 to 3.06)
Stillbirth	0 (0.0)	1,416 (0.1)	...
Perinatal mortality	≤ 5 (≤ 2.7)	7,320 (0.4)	1.38 (0.20 to 9.51)
Neonatal death	≤ 5 (≤ 2.7)	15,858 (0.8)	1.90 (0.62 to 5.87)

\* All incidence proportion ratios are unadjusted, estimated from log-binomial models using generalized estimating equations to account for within-mother clustering from additional pregnancies during follow-up. Ellipses indicate failure to estimate incidence proportion ratios due to zero events in the AKI-D group.

† To comply with privacy regulations for minimizing the chance of identification of a study participant, numbers of participants are suppressed in the case of 5 or fewer participants (reported as ≤5), however data was analyzed based on a value of 5 for the purpose of reporting an approximate incidence proportion ratio for perinatal complications. Incidence proportion ratios may be overestimated in these groups.

Several perinatal complications were more likely to occur in pregnancies complicated by AKI-D compared to those without AKI-D, including low birth weight (IPR 4.66, 95% CI 3.64 to 5.96), small for gestational age (IPR 3.16, 95% CI 1.90 to 5.27), and preterm birth (IPR 2.49, 95% CI 2.06 to 3.06). However, AKI-D was not associated with more severe perinatal complications such a stillbirth, perinatal mortality, and neonatal death.

## 6.5 Maternal Outcomes of AKI-D

The proportion of pregnancies resulting in maternal mortality and chronic dialysis dependence in relation to AKI-D status are reported in Table 11.

**Table 11: Incidence of maternal mortality and chronic dialysis dependence among pregnancies with and without AKI-D**

Maternal Outcome, <i>n</i> (%)	AKI-D <i>n</i> =188	No AKI-D <i>n</i> =1,918,601	<i>P</i> value *
Maternal Mortality	8 (4.3)	229 (0.01)	< 0.001
Chronic Dialysis Dependence †	7 (3.9) ‡		

\* *P* values represent the difference in unadjusted relative risk of the specified maternal outcome associated with the presence (vs. absence) of AKI-D in pregnancy. This was estimated from log-binomial models using generalized estimating equations to account for within-mother clustering from additional pregnancies during follow-up. The unadjusted relative risk was not reported due to the unstable estimate as a result of the large difference in proportion of mortality events between the two groups (eg. RR 356.51, 95% CI 178.76 to 711.00).

† Chronic dialysis dependence was not relevant in the group without AKI-D.

‡ Refers to the 180 (95.7%) pregnancies complicated by AKI-D in which the mother survived beyond 90 days.

Among the 188 pregnancies complicated by AKI-D, eight women (4.3%) died within 90 days of delivery, compared with 229 (0.01%) maternal deaths in the group without AKI-D ( $P < 0.001$ ) (Table 11). The absolute risk difference of maternal mortality between the two groups is 4.24% (95% CI 1.36 to 7.13). Listed causes of death included severe preeclampsia, pregnancy-related liver or biliary tract disorders, hemorrhage, and complications of obstetric surgery. Among the 180 pregnancies in which the mother survived beyond 90 days, seven (3.9%) women remained dependent on chronic dialysis after 90 days postpartum (Table 11).

## Chapter 7

### 7 Discussion

#### 7.1 Main Findings

In this study of 1.9 million pregnancies over a 15-year period, 1 in 10,000 pregnancies were affected by AKI-D. Most women who developed AKI-D had no record of a preexisting chronic medical condition such as hypertension, diabetes, or chronic kidney disease. Several maternal complications were associated with a higher incidence of AKI-D in pregnancy or the postpartum period. These included preeclampsia, thrombotic microangiopathy, pyelonephritis, sepsis, caesarean delivery, and postpartum hemorrhage. AKI was associated with a higher incidence of adverse perinatal complications including low birth weight, small for gestational age, and preterm birth, however there were no stillbirths and no more than five neonatal deaths (< 3%) in affected pregnancies. Maternal mortality after AKI-D was 4%, and 4% of survivors remained dependent on dialysis after delivery.

#### 7.2 Comparison with Other Studies

##### 7.2.1 Incidence of AKI-D

Most population-based reports on pregnancy-related AKI refer exclusively to secular trends in infection-related first-trimester AKI, coinciding with the legalization of abortion and improved obstetrical care in low-income countries.<sup>1,52-55</sup> Pregnancies in high-income regions are more frequently complicated by hypertensive disorders of pregnancy, gestational diabetes, and postpartum hemorrhage, whereas genitourinary and obstetric infections appear to be on the decline.<sup>7</sup> More recent North American studies examining the impact of these trends on AKI defined by hospital diagnosis codes, indicate a paradoxical increase in the incidence of AKI in pregnancy from what was previously reported, with an incidence proportion of approximately 2 in 10,000 deliveries.<sup>39,40,56</sup> This trend has been attributed to the increasing incidence of hypertensive disorders of pregnancy in these populations.<sup>56</sup> While AKI-D occurred much less frequently in our population (1 in 10,000 deliveries), our data suggest that these complications, alone or in



combination with other risk factors, may occur in a setting necessitating acute dialysis as well.

### 7.2.2 Maternal Complications Associated with AKI-D

Trends indicating an increasing incidence of AKI in North America appear to correspond to increases in the rate of deliveries among women at advanced maternal age or with pre-existing medical conditions such as hypertension, diabetes mellitus, and chronic kidney disease (known risk factors for preeclampsia)<sup>59,60</sup> and those with complications such as preeclampsia and postpartum hemorrhage noted in other population-based studies.<sup>7</sup> These, and other complications including sepsis, cardiac failure, and caesarean section have been confirmed to be associated with AKI in pregnancy, however the temporal increase in AKI in pregnancy reported in previous North American studies appears to be restricted to pregnancies complicated by hypertensive disorders, and was especially pronounced among women with preeclampsia.<sup>56</sup>

Women who developed AKI-D in our cohort were generally healthy with few recorded pre-existing medical conditions. However, as the prevalence of preexisting medical conditions in our study was likely underestimated, women with chronic hypertension and preexisting chronic kidney disease may drive a greater proportion of AKI-D events than realized herein.<sup>7,8</sup> In addition to preeclampsia, we identified several other maternal characteristics that alone or in combination may be associated with an increased incidence of AKI-D. These include thrombotic microangiopathy, pyelonephritis, sepsis, caesarean delivery, and postpartum hemorrhage. While it was beyond the scope of this research to determine the nature of these associations, many of these complications have been highlighted as associative factors in previous studies and could be assumed to be either directly causal of AKI (eg. preeclampsia, thrombotic microangiopathy, pyelonephritis, sepsis, postpartum hemorrhage) or occur as a result of the AKI episode or its complications (eg. caesarean delivery), based on known pathophysiologic mechanisms of AKI.<sup>38,56,69</sup>

### 7.2.3 Perinatal Complications of AKI-D

No prior studies have assessed the incidence of perinatal complications in relation to pregnancy-related AKI; therefore it is unclear whether associated perinatal complications such as low birth weight, small for gestational age, and preterm birth may be attributed to the AKI-D event itself or to associated acute medical complications. Further, it is impossible to separate out the effect of AKI from the dialysis treatment with our data. However, early delivery as a result of deteriorating maternal condition and altered uteroplacental hemodynamics could explain this finding in either case.<sup>105</sup>

### 7.2.4 Maternal Outcomes of AKI-D

Recent reports of severe cases of pregnancy-related AKI are limited to two small studies from Brazil and Egypt, in which AKI was defined by treatment with dialysis and RIFLE criteria within admission to the intensive care unit respectively.<sup>38,69</sup> These studies suggest that maternal mortality may be as high as 30% in more severe cases of AKI, with up to 50% of women remaining dependent on dialysis after delivery.<sup>38,69</sup> In contrast to these studies, our data suggest that although AKI events during pregnancy do occur more frequently in the context of acute medical complications, the impact may be short-lived. Maternal mortality in our study was only 4.3% (compared with 0.01% in the general population) and fewer than 4% of survivors were dependent on dialysis after 12 weeks postpartum. Accounting for differences in severity of AKI, this is in keeping with the 2.8% incidence proportion of maternal death reported in previous population-based studies of AKI in pregnancy in Canada.<sup>56</sup> However, dialysis dependence was not assessed in these studies.

Although our results support a strong association between AKI-D and maternal mortality, the absolute risk of death is low. This, and the low proportion of survivors remaining dialysis dependent, should be viewed as reassuring when considering the overall impact of AKI-D on the population. Interpretation of the relative differences in risk of maternal mortality in this setting would require further exploration of the causal association between AKI-D and mortality, which was beyond the scope of this study.

## 7.3 Strengths

The lack of a consensus definition for AKI in pregnancy and variations in demographics and standard of care among populations has made estimation of the current incidence of pregnancy-related AKI from epidemiologic studies difficult.<sup>1,39,40,52–56</sup> Efforts to examine the maternal and perinatal complications in relation to pregnancy-related AKI in contemporary population-based cohorts is limited.<sup>39,40,56</sup> To our knowledge, this is the first population-based study to characterize the incidence of AKI-D in pregnancy and its correlates and outcomes in a developed nation without apparent selection bias or loss to follow-up, containing over three times the number of cases treated with dialysis as in other reports.<sup>69</sup> We were able to do this by using novel linkages between maternal and infant administrative data.

## 7.4 Limitations

The limitations of this study are outlined below.

### 7.4.1 Generalizability

The definition of AKI was restricted to those treated with dialysis, so these results may not apply to less severe presentations of AKI in pregnancy. Further, because the analytic cohort was limited to pregnancies that resulted in a live birth or stillbirth after 20 weeks gestation, study results are not generalizable to pregnancies resulting in an early pregnancy loss.

### 7.4.2 Information Bias

The presence and strength of associations observed in epidemiologic studies are a function of the validity of study variables. We conducted our analysis using hospital diagnostic and physician billing codes from administrative data. Our strategy for identifying many of the maternal indicators with these codes may lack sensitivity and, therefore, underestimate their true prevalence. In most cases, misclassification of these variables is expected to be non-differential as it is independent of AKI-D status and would be expected to bias measures of association between the presence (vs. absence) of these characteristics and incidence of AKI-D towards the null hypothesis (Type II

error).<sup>84</sup> Although some coding algorithms may also lack specificity. For example, codes used to ascertain ‘thrombotic microangiopathy’ may capture cases of preeclampsia and HELLP syndrome, in addition to thrombotic thrombocytopenic purpura, given the lack of specificity of both the terminology and codes.

Assuming a 42-week gestation for the purposes of defining the onset of pregnancy may have contributed to misclassification of pre-pregnancy maternal characteristics as pregnancy-related complications for preterm deliveries. However, most maternal characteristics ascertained during pregnancy are complications (and codes) specific to pregnancy (eg. multifetal gestation, hyperemesis gravidarum, gestational hypertension, preeclampsia, thrombotic microangiopathy) or would be expected to preclude conception of a viable pregnancy (eg. thrombotic microangiopathy, pyelonephritis, sepsis). Therefore, this misclassification should be limited.

Additional sources of information bias include lack of access to clinical parameters at the time of dialysis initiation, including renal function, blood pressure, and basis for starting or stopping dialysis, so women with progressive chronic kidney disease initiating dialysis electively during pregnancy to optimize maternal and fetal wellbeing could have been misclassified as having AKI-D in this study. However, the low prevalence of preexisting chronic kidney disease and low proportion of women that remained dialysis dependent postpartum suggests that this was infrequent. Further, defining AKI by treatment with dialysis precludes our ability to isolate the independent effects of AKI from the dialysis treatment itself.

### 7.4.3 Confounding

There are several associations noted in this study that could be explored further. These include associations between various medical complications of pregnancy and the incidence of AKI-D, AKI-D and the incidence of various perinatal complications, and AKI-D and the risk of adverse maternal outcomes. However, as described in Section 3.3, the complex (and in many cases, causal) relationship between pre-pregnancy maternal characteristics, medical complications of pregnancy, perinatal complications, and adverse maternal outcomes precludes our ability to isolate potential confounders to incorporate

into multivariable logistic regression models to further explore these associations. Further, our study was underpowered for such analyses due to the low event rate of AKI-D in our cohort and lack of sensitivity of coding algorithms used to ascertain maternal characteristics of interest. For this reason, results of these analyses should be viewed as hypothesis generating and confirmed in future studies.

## 7.5 Recommendations for Future Research

As a direct extension of this research, additional studies could be performed to confirm the independent association between several maternal characteristics in this study and the risk of AKI in pregnancy. However, there are several other knowledge gaps in this area that warrant further attention. Additional research is needed to establish a method of early and specific diagnosis of AKI in pregnancy, perhaps using renal biomarkers that are independent of serum creatinine, a late indicator of acute kidney injury in pregnancy.<sup>106</sup> Finally, although experience from treatment of pregnant women with end-stage renal disease suggests that intensified hemodialysis and frequent maternal and fetal surveillance might be the key to further improving maternal and perinatal outcomes in AKI settings as well, the threshold for initiation needs further consideration. Unfortunately, given the infrequency with which this condition occurs, it is unlikely there will ever be controlled trials in this area. Large observational studies using administrative data or a network meta-analysis, combining administrative data from multiple provinces, could be used to provide insight into this treatment decision.

## 7.6 Conclusion

This study confirms that AKI treated with dialysis in pregnancy is rare and typically occurs in otherwise healthy women who acquire a major pregnancy-related medical condition. While assessment for comorbid conditions such as hypertension, diabetes, and chronic kidney disease, remains central to identifying women at risk for hypertensive disorders of pregnancy, our data suggest that severe AKI may be occurring through a variety of physiologic mechanisms that may not be predictable from pre-pregnancy health status. Fortunately, with ongoing improvements in obstetrical care, multidisciplinary approaches, and new insights into the diagnosis and management of

associated conditions such as preeclampsia, maternal and perinatal mortality in this setting are largely avoidable. Knowledge of associated characteristics and outcomes presented in this study provide important prognostic information for patients and a framework for physicians to understand severe pregnancy-related AKI in the current era and inform strategies that better identify women at risk.

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## Appendices

### Appendix A: Checklist of Recommendations for Reporting of Observational Studies Using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Guidelines

	Item No.	Recommendation	Reported
<b>Title and Abstract</b>			
Title / abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Title, Abstract
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
<b>Introduction</b>			
Background / rationale	2	Explain the scientific background and rationale for the investigation being reported	Chapters 1-3
Objectives	3	State specific objectives, including any pre-specified hypotheses	Chapter 4
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	Chapter 5
Setting	5	Describe the setting, locations and relevant dates, including periods of recruitment, exposure, follow-up and data collection	Chapter 5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Chapter 5
		(b) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders and effect modifiers. Give diagnostic criteria, if applicable	Chapter 5
Data sources / measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Chapter 5
Bias	9	Describe any efforts to address potential sources of bias	Chapter 5
Study size	10	Explain how the study size was arrived at	Chapter 5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Chapter 5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Chapter 5
		(b) Describe any methods used to examine subgroups and interactions	Chapter 5
		(c) Explain how missing data were addressed	Chapter 5
		(d) If applicable, explain how loss to follow-up was addressed	Not applicable
		(e) Describe any sensitivity analyses	Not applicable
<b>Results</b>			
Participants	13	(a) Report numbers of individuals at each stage of study—	Chapter 6



		e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	
Descriptive data	14	(b) Give reasons for nonparticipation at each stage	Chapter 6
		(c) Consider use of a flow diagram	Chapter 6
		(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	Chapter 6
Outcome data	15	(b) Indicate number of participants with missing data for each variable of interest	Chapter 5
		(c) Summarize follow-up time (e.g. average and total amount)	Chapter 6
		Report numbers of outcome events or summary measures over time	Chapter 6
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Chapter 6
		(b) Report category boundaries when continuous variables were categorized	Chapter 6
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Chapter 6
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	Not applicable
<b>Discussion</b>			
Key results	18	Summarize key results with reference to study objectives	Chapter 7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Chapter 7
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Chapter 7
Generalizability	21	Discuss the generalizability (external validity) of the study results	Chapter 7
<b>Other Information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Acknowledgements

## Appendix B: Data creation plan

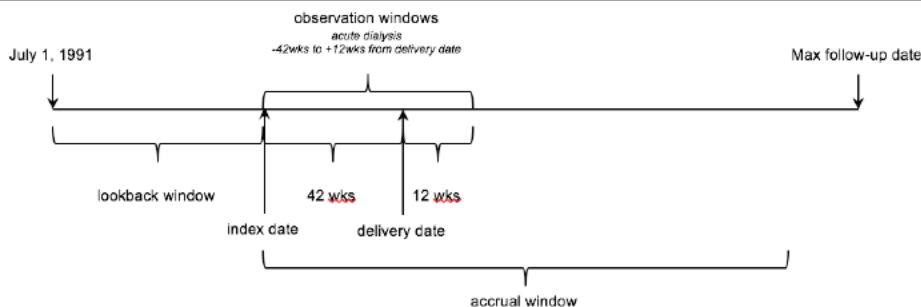
<b>Characteristics and Outcomes of Acute Kidney Injury Treated with Dialysis During Pregnancy and the Postpartum Period Design: Retrospective Cohort Study</b>	
<b>Study Number</b>	2013 0900 381 000
<b>Research Program</b>	Kidney Dialysis Transplantation
<b>ICES PI</b>	Amit Garg
<b>Person Responsible</b>	Ainslie Hildebrand
<b>PIA Approval</b>	Yes
<b>Most Recent Update</b>	Version 22: June 10, 2014 (AH)
<b>List of Datasets Used</b>	<ol style="list-style-type: none"> <li>1. <b>OHIP</b> <ul style="list-style-type: none"> <li><u>Claim Type</u></li> <li><input checked="" type="checkbox"/> Non-lab claims</li> <li><u>Code Types</u></li> <li><input checked="" type="checkbox"/> Fee codes</li> <li><input checked="" type="checkbox"/> Diagnosis codes</li> </ul> </li> <li>2. <b>CIHI-DAD</b> <ul style="list-style-type: none"> <li><u>Source</u></li> <li><input checked="" type="checkbox"/> Inpatient</li> <li><input checked="" type="checkbox"/> Same day surgery</li> <li><u>Institution types</u></li> <li><input checked="" type="checkbox"/> Acute care (insttype = 'AP' or 'AT')</li> </ul> </li> <li>3. <b>RPDB</b></li> <li>4. <b>MOMBABY</b> [uses CIHI-DAD]</li> <li>5. <b>Ontario Diabetes Database</b></li> <li>6. <b>Ontario Hypertension Database</b></li> <li>7. <b>Ontario Registrar General - Death (Vital Stats)</b></li> </ol>
<b>Coding Details</b>	<p><i>Specific variable definitions are in coding appendix attached.</i></p> <ol style="list-style-type: none"> <li>1. <b>Diagnostic codes</b> <ul style="list-style-type: none"> <li><u>Diagnosis Type (dxtype)</u></li> <li><input checked="" type="checkbox"/> All (alldx)</li> <li><u>Study period</u></li> <li><input checked="" type="checkbox"/> Prior to 2002 fiscal year → ICD-9 CODES</li> <li><input checked="" type="checkbox"/> From 2002 fiscal year and onwards → ICD-10 CODES</li> <li><u>Include suspected/questionable diagnoses?</u></li> <li><input checked="" type="checkbox"/> No</li> </ul> </li> <li>2. <b>Procedure codes</b> <ul style="list-style-type: none"> <li><u>Include abandoned procedures?</u></li> <li><input checked="" type="checkbox"/> No</li> <li><u>Study period</u></li> <li><input checked="" type="checkbox"/> Prior to 2002 fiscal year → CCP CODES</li> <li><input checked="" type="checkbox"/> From 2002 fiscal year and onwards → CCI CODES</li> </ul> </li> <li>3. <b>Look-back period</b> <ul style="list-style-type: none"> <li><u>Reference date</u></li> <li><input checked="" type="checkbox"/> Do not include index date in look-back period (stop at index-1)</li> </ul> </li> </ol>
<b>Cohort Creation</b>	
<b>Index Event</b>	Pregnancy resulting in childbirth, defined by a valid b_bdate in the MOMBABY dataset. <b>Delivery date</b> = date of childbirth (b_bdate) <b>Index date</b> = assumed onset of pregnancy (b_bdate minus 42 weeks)
<b>Inclusion Criteria</b>	All pregnancies resulting in childbirth, defined by a valid b_bdate in the MOMBABY dataset.

**Exclusions****Data Cleaning**

1. Exclude any index event based on the following characteristics (apply criteria sequentially):
  - a) Invalid m\_IKN
  - b) Missing m\_key
  - c) Missing b\_key
  - d) Missing age or sex data for mother in RPDB
  - e) Maternal sex = male in RPDB
  - f) Mothers age less than 10 years or greater than 60 years on delivery date (using age from %getdemo)
  - g) Date of mothers death is greater than 5 days prior to the delivery date (dthdate > [delivery date - 5])
  - h) Any b\_bdate within 3 and 140 days of the previous b\_bdate for the same m\_IKN (it would be impossible for a mother to carry 2 viable pregnancies during this time frame)
  - i) Keep the only the first pregnancy if b\_bdate with in 2 days of the previous b\_bdate for the same m\_IKN and flag as multiple birth
2. Apply criteria for dealing with complicated records in MOMBABY dataset as outlined below and exclude as indicated.  
 MOMBABY dataset (which uses the CIHI-DAD) should, in theory, not have duplicate birth records. However, there may still be cases where the same mom (IKN) has 2 m\_keys, with MULTIBIRTH=True to signify multiple births. Alternatively, there may be records with multiple m\_keys with MULTIBIRTH=False or other atypical circumstances that make it difficult to determine the details of each pregnancy resulting in childbirth. Use the following criteria to identify index events and index dates:
  - a) If one m\_key links to one b\_key (associated with one b\_bdate), include as index event and use b\_bdate as delivery date.
  - b) If one m\_key links to more than one b\_key (each associated with a b\_bdate), include as index event and use earliest b\_bdate as delivery date
  - c) If more than one m\_key links to the same b\_key (associated with one b\_bdate), regardless of the gap between the m\_admdates, then randomly select an m\_key and discard the other m\_key(s)

**Defines Population**

3. Evidence of chronic dialysis, defined by the presence of a chronic dialysis code within the 5 years prior to index date.
4. Evidence of a kidney transplantation code within the 5 years prior to index date.

**Time Frame Definitions**

**Accrual Window** The accrual window for index events is January 1, 1997 to December 31, 2011.

**Follow-Up** The end of the follow-up period is March 31, 2012 (12 weeks after last possible delivery date).

**Lookback Window** Look back five years from index date for exclusions (fixed 5-year look back window for each index event). The earliest possible lookback will be July 1, 1991.

<b>Observation Window</b>	Varies depending on outcome. Refer to outcome definitions below.
<b>Observation Window Termination</b>	<p>Observation window terminates with any of the following:</p> <ol style="list-style-type: none"> <li>1. From delivery date to 120 days after the delivery date depending on outcome assessed</li> <li>2. March 31, 2012 (maximum follow-up date)</li> <li>3. Death</li> </ol>
<b>Variable Definitions</b>	
<b>Outcome Definitions</b>	<ol style="list-style-type: none"> <li>1. <b>Acute kidney injury treated with dialysis (AKI-D):</b> Defined by a maternal hospital admission including <math>\geq 1</math> acute dialysis code between index date and 12 weeks after the delivery date. <p>Timing definitions to classify primary outcome by trimester:            (Use OHIP Fee Codes alone to report the absolute number of pregnancies complicated by AKI by Trimester [as timing not reliable for CCP and CCI codes and this is for internal use only]. Use 1<sup>st</sup> acute dialysis code for each pregnancy to define timing of this outcome and count each pregnancy only once.)</p> <p><i>1<sup>st</sup> Trimester:</i> outcome occurs from index date to 30 weeks before the delivery date  <i>2<sup>nd</sup> Trimester:</i> outcome occurs from 29 weeks and 6 days before the delivery date to 15 weeks before the delivery date  <i>3<sup>rd</sup> Trimester:</i> outcome occurs from 14 weeks and 6 days before the delivery date to the day prior to the delivery date  <i>Postpartum:</i> outcome occurs from the delivery date to 12 weeks after the delivery date</p> </li> <li>2. <b>90-day mortality:</b> Defined by a maternal dthdate recorded in RPDB between the delivery date and 90 days after the delivery date.            Note primary or immediate cause of death using 'COD_IMMEDIATE' (until 2002) or 'COD_PRIMARY' in ORGD (from 2003)</li> <li>3. <b>Chronic dialysis:</b> Defined by i) absence of death, AND ii) the presence of a maternal dialysis code on at least two separate days between 90 and 120 days after the delivery date.</li> </ol>
<b>Maternal/Perinatal Characteristics</b>	<p><b>Maternal Characteristics Prior to Delivery</b></p> <ol style="list-style-type: none"> <li>1. Age at delivery date, from RPDB (<i>differences in maternal age exist between MOMBABY and RPDB - selected RPDB to define maternal age given entry errors present in MOMBABY</i>) <ul style="list-style-type: none"> <li>• Mean (SD)</li> <li>• Median (IQR)</li> <li>• Range (Min - Max)</li> <li>• By category (&lt;20, 20-29, 30-39, 40+)</li> </ul> </li> <li>2. Neighborhood income, on delivery date, from RPDB <ul style="list-style-type: none"> <li>• Categorize quintiles in three groups: 1-2, 3 [referent], 4-5</li> <li>• Report missing data separately</li> </ul> </li> <li>3. Rural residence, on delivery date, from RPDB <ul style="list-style-type: none"> <li>• Report missing data separately</li> </ul> </li> <li>4. Previous pregnancies from same mother, between 1991 and delivery date <ul style="list-style-type: none"> <li>• Mean (SD)</li> <li>• Median (25<sup>th</sup>, 75<sup>th</sup> percentile)</li> <li>• Range (Min - Max)</li> <li>• By category (0, 1, 2+)</li> </ul> </li> <li>5. Years since previous pregnancy, between 1991 and delivery date</li> </ol>

- 
- Mean (SD)
  - Median (25<sup>th</sup>, 75<sup>th</sup> percentile)
  - Range (Min – Max)
6. Hypertension, within 5 years prior to index date
  7. Diabetes mellitus, within 5 years prior to index date
  8. Chronic kidney disease, within 5 years prior to index date
  9. General practitioner/family physician consultation, within 5 years prior to index date
  10. Internal medicine specialist consultation, within 5 years prior to index date
  11. Nephrologist consultation, within 5 years prior to index date

### **Maternal Characteristics During Pregnancy or the Postpartum Period**

*To be determined between the index date and 12 weeks after delivery date.*

1. Multifetal gestation, defined by [m\_multiple birth=T or b\_multiple birth=T] in mother or infant record in MOMBABY dataset. All other pregnancies are assumed to be singletons.
2. Hyperemesis gravidarum
3. Gestational hypertension
4. Preeclampsia
5. Thrombotic microangiopathy
6. History of thrombotic microangiopathy (TMA) requiring plasma exchange, defined by any of the following:
  - a) The receipt of PLEX (by OHIP fee codes) that falls within an admission for TMA (using CIHI codes)
  - b) The receipt of PLEX (by OHIP fee codes) that is preceded by a TMA code (using OHIP dx codes) within 7 days. Use the PLEX code that is closest to the TMA code to define this interval.
  - c) The receipt of PLEX (by OHIP fee codes) that is preceded by a TMA code (using OHIP dx codes) within 7 days. Use the PLEX code that is closest to the TMA code to define this interval.
6. Pyelonephritis
7. Sepsis
8. Caesarean delivery
9. Postpartum hemorrhage

### **Perinatal Characteristics**

*Differences in infant birthdate exist between MOMBABY and RPDB – selected MOMBABY to define infant birthdate given many missing b\_ikns required to link to RPDB*

1. Low birthweight: Defined by a weight of less than 2500g for the variable [WEIGHT] in the infant record (b\_key) in the MOMBABY/CIHI dataset. Assess on delivery date  
Look at data carefully, as may need to troubleshoot errors in data entry (kilograms vs. grams): a '0' preceding the number (eg. 0900) implies that weight reported in kilograms (eg. 90.0 kg), however many of these values may in fact be reported in grams (eg. 900g). If value  $\geq 0100$ , interpret as grams (eg. 100g). If value  $< 0100$ , interpret as kilograms (eg. 10.0 kg) and use 0001 as the lowest possible birthweight allowed (eg. 0.1 kg or 100g).
  2. Small for gestational age/Intrauterine growth restriction: Defined by codes in the m\_ikn, b\_ikn, or b\_key. Assess from delivery date to 12 weeks after the index date
  3. Premature birth: Defined as birth before 37 weeks of gestation using [m\_gestwks\_del and b\_gestwks\_del] in mother and infant record in MOMBABY dataset respectively where [b\_stillbirth=F and m\_stillbirth=F] or the presence of a Prematurity/LowBirthweight code. Preferentially use infant data source unless it is missing, in which case use mother data source. The
-

[m\_gestwks\_del and b\_gestwks\_del] variable only became available in MOMBABY dataset in 2002. Assess on delivery date.

4. Stillbirth: Defined by [b\_stillbirth=T or m\_stillbirth=T] in the infant and maternal records in the MOMBABY dataset respectively. Assess on delivery date.
5. Perinatal mortality: Defined by death of infant within 7 days of birth from RPDB or CIHI (using b\_ikn or b\_key) or stillbirth. Stillbirth is defined by [b\_stillbirth=T or m\_stillbirth=T] in the infant and maternal records in the MOMBABY dataset respectively. Assess from delivery date to 7 days after delivery date
6. Neonatal death: Defined by death of infant within 28 days of birth from RPDB or CIHI (using b\_ikn or b\_key), when [b\_stillbirth=F and m\_stillbirth=F]. Assess from delivery date to 28 days after the delivery date.

### Analysis

#### Outputs and Analysis

Calculate 95% confidence intervals for all proportions and set the level of significance at  $P < 0.05$ .

#### 1. Cohort creation

- Use specified inclusion and exclusion criteria to create the pregnancy cohort. Report number of pregnancies included and excluded at each step.

#### 2. Cluster information

- Determine the number of unique mothers and number of pregnancies/mother.

#### 3. Incidence proportion of AKI-D

- Report the proportion of all pregnancies that fulfilled the outcome definition of AKI-D.

#### 4. Maternal characteristics

- Report descriptive statistics for each maternal characteristic prior to delivery for the entire cohort, AKI-D group, and non-AKI-D group.
- Report the standardized difference to compare maternal characteristics in pregnancies with and without AKI-D.

#### 5. Incidence of AKI-D according to maternal complications

- Use generalized estimating equations and log-binomial models to estimate the relative difference in the incidence of AKI-D associated with the presence (vs. absence) of each maternal complication. Report the unadjusted incidence proportion ratio and 95% confidence interval.

#### 6. Incidence of perinatal complications according to AKI-D status

- Use generalized estimating equations and log-binomial models to estimate the relative difference in the incidence of perinatal complications associated with the presence (vs. absence) of AKI-D. Report the unadjusted incidence proportion ratio and 95% confidence interval.

#### 7. Maternal outcomes

- Report the proportion of pregnancies in each group that fulfilled the maternal outcome definition of 90-day mortality.
- For pregnancies complicated by 90-day mortality in the AKI-D group, document the cause of death.
- Use generalized estimating equations and log-binomial models to estimate the relative risk of maternal mortality associated with the presence (vs.

---

absence) of AKI-D. Report the risk difference with 95% confidence interval and the unadjusted relative risk with 95% confidence interval and P-value.

- Report the proportion of pregnancies in the AKI-D group that fulfilled the maternal outcome definition of chronic dialysis dependence.
-

## Appendix C: Institute for Clinical Evaluative Sciences project-specific privacy impact assessment form

ICES Privacy Impact Assessment Form	Version 2.0 September 3, 2010
<b>INSTITUTE FOR CLINICAL EVALUATIVE SCIENCES PROJECT-SPECIFIC PRIVACY IMPACT ASSESSMENT FORM (FOR ALL ICES PROJECTS)</b>	
JUL 20 2012	
<b>A. PROJECT TITLE</b>	
Secular trends in pregnancy-related acute kidney injury.	
<b>B. THE PROJECT</b>	
Select the PHIPA Section that applies to this project as the privacy implications are different.	
<b>1) Please indicate below whether this Project falls into PHIPA Section 45i and/or 45ii OR Section 44(iii). (see "Completing PIAs" document and/or Reference")</b>	
<b>Section 45:</b>	
i) The purpose of the project is analysis or compiling statistical information related to evaluation, monitoring, planning, resource allocation, service delivery and management of the health care system;	<input checked="" type="checkbox"/> Y    Sec. 45 i)
<i>and/or</i>	
ii) This project is creating infrastructure or a framework for the activity above?	<input type="checkbox"/> Y    Sec. 45 ii)
<i>or</i>	
<b>Section 44:</b>	
iii) Research purpose other than activities listed in Section 45 above <small>(see "Completing PIAs" document or contact Privacy Office).</small>	<input type="checkbox"/> Y    Sec. 44 iii)
<b>2) Has an electronic PIA and Proposal been submitted to the Program Administrator? (A DCP may be an acceptable substitute in some circumstances)</b>	
<input checked="" type="checkbox"/> Y	
<b>3) Is data planned for use in this project to be linked with other data sets?</b>	
<input checked="" type="checkbox"/> Y	
<b>4) Is the rationale for the planned data linkage described in the proposal (or in the DCP)? If not, please append.</b>	
<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<b>5) From a Process and/or Technology perspective, is this project :</b>	
<ul style="list-style-type: none"> <li>• Introducing a novel methodology or direction?</li> <li>• Introducing significant changes from an existing project?</li> <li>• Implementing a new remote implementation?</li> <li>• Introducing a new technology?</li> </ul>	<input type="checkbox"/> Y <input type="checkbox"/> Y <input type="checkbox"/> Y <input type="checkbox"/> Y
<small>If yes, security consultation with CISO may be of benefit for this project</small>	
<b>6) Is this a trainee / student / fellow project?</b>	
<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<b>7) If you answered "yes" in question 6, please identify the student's designation below:</b>	
<input type="checkbox"/> MSc <input type="checkbox"/> PhD <input checked="" type="checkbox"/> Other <u>MD, MSc candidate</u>	



8) Name the project participants / staff and provide contact details here.  
**Use pull-down lists** under role to describe each person's activity.

At least one ICES scientist must be named for all projects as Investigator or Co-investigator.  
**Include affiliations/qualifications for all scientists who are not ICES scientists/adjunct scientists.** You may provide affiliations/qualifications on an attached sheet or electronically.

NAME / AFFILIATION/ QUALIFICATIONS	ROLE	PHONE	E-MAIL
Amit Garg / UWO / MD PhD	PI	[REDACTED]	[REDACTED]
Ainslie Hildebrand / UWO / MD	Student	[REDACTED]	[REDACTED]
Jagdish Rangrej / ICES / MSc	PB	[REDACTED]	[REDACTED]
Salimah Shariff / ICES / PhD	PB	[REDACTED]	[REDACTED]
	PI		
	PI		
	PI		
	PI		
	PI		
	PI		
	PI		
	PI		
	PI		
	PI		

9) Please name team members who will have access to the individual-level data.  
 (Have you provided names and related qualifications as requested above?)

Jagdish Rangrej, P&B Assigned Analyst Salimah Shariff, P&B Assigned Analyst Ainslie Hildebrand, Student	[REDACTED]
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ICES Privacy Impact Assessment Form

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- 10) What types of data are being used? (check all that apply)  
Identify those which are being linked to administrative datasets.

Type	To be linked
<input checked="" type="checkbox"/> ICES Administrative Data	
<input type="checkbox"/> Survey	<input type="checkbox"/>
<input type="checkbox"/> Registry	<input type="checkbox"/>
<input type="checkbox"/> Primary clinical	<input type="checkbox"/>
<input type="checkbox"/> Chart abstraction	<input type="checkbox"/>
<input type="checkbox"/> Electronic Health Record	<input type="checkbox"/>
<input type="checkbox"/> Web-based data collection	<input type="checkbox"/>
<input type="checkbox"/> Other: (Please indicate below)	<input type="checkbox"/>

- 11) What databases are being used? (check all that apply)  
Indicate dates of data to be used. (Note: Year means year for which data is summarized.  
Fiscal year is defined as: 1 April 2008 – 31 March 2009 = fiscal 2008.

Type	Fiscal year
<b>Administrative Databases</b>	
<input checked="" type="checkbox"/> CIHI-DAD	1991 to 2011
<input type="checkbox"/> CIHI-SDS	to
<input type="checkbox"/> CIHI-NACRS	to
<input type="checkbox"/> CIHI-CCRS	to
<input type="checkbox"/> CIHI-NRS	to
<input type="checkbox"/> ODB	to
<input checked="" type="checkbox"/> OHIP	1991 to 2011
<input type="checkbox"/> HCD	to
<input type="checkbox"/> LOC	to
<input type="checkbox"/> OMHRS	to
<input checked="" type="checkbox"/> RPDB	N/A
<input type="checkbox"/> CAPE	N/A
<input type="checkbox"/> IPDB	N/A
<input type="checkbox"/> CPDB	N/A
<input type="checkbox"/> Other	
<input type="checkbox"/>	
<input type="checkbox"/>	
<b>Composite Databases (i.e., OHIP + CIHI + ODB)</b>	
<input type="checkbox"/> Asthma*	
<input type="checkbox"/> CHF *	
<input type="checkbox"/> COPD*	
<input type="checkbox"/> Hypertension	
<input checked="" type="checkbox"/> MOMBaby	
<input checked="" type="checkbox"/> ODD	
<input type="checkbox"/> OMID	
<input type="checkbox"/> PIBD*	
<input type="checkbox"/> Other	
<input type="checkbox"/>	

\* Permission/notification required before use of asterisked datasets. Please contact Director, Information Management for details.

Restricted Databases – Registry – Permission Required	
<input type="checkbox"/> CCN* (approval required)	to
<input type="checkbox"/> OCR** (approval required)	to
<input type="checkbox"/> RCSN † (approval required)	to
<input type="checkbox"/> EFFECT*(approval required)	to
<input type="checkbox"/> OBSP** (approval required)	
<input type="checkbox"/> Cytobase** (approval required)	
Others: (Please indicate below)	
	to
	to

\* Note: all studies planning use of CCN data must be approved by an external process through Program Lead - CardioDIP  
 \*\* All studies planning use of Cancer Care Ontario databases (ie, OCR, OBSP, Cytobase) must be logged and submitted to Cancer Care Ontario by Chief Privacy Officer (contact for details) and approved by additional process.  
 † Written application for use of Stroke Data is required  
 \*Written application / approval required by Program Lead - CardioDIP

Surveys	Linked
<input type="checkbox"/> OHS*	<input type="checkbox"/>
<input type="checkbox"/> NPHS*	<input type="checkbox"/>
<input type="checkbox"/> CCHS*	<input type="checkbox"/>
<input type="checkbox"/> PCAS	<input type="checkbox"/>
<input type="checkbox"/> OTHER:	<input type="checkbox"/>

\* Restricted to MOHLTC mandated and/or funded projects.

Other Databases	Year
<input type="checkbox"/> ARIS	to
<input type="checkbox"/> MIS	to
<input type="checkbox"/> OTR	to
<input type="checkbox"/> Custom Clinical dataset	to
<input type="checkbox"/> Others: (Please indicate below)	
	to

- 12) i) Is probabilistic linkage planned?  Y  N
- ii) Please list any personal health information/data that will be collected and / or used in this study, which *potentially*, alone or *in combination*, could be associated with *increased risk to privacy* (identification of the individual).
- Birth date     Postal Code     Other (list below)

**C. DATA SECURITY/PRIVACY IMPACT**

**A. Internal Projects:**

- 1) Complies with all ICES policies / procedures  Y

Describe perceived need for modification:

None

ICES Privacy Impact Assessment Form

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**B. External Projects (e.g. Chart abstraction, EHM/EMR, primary data collection) have special privacy and security data concerns.**

**ICES Staff Research Coordinator and/or Analyst should be designated for these projects.**

- 1) Complies with all ICES policies / procedures  Y  
Describe perceived need for modification:

- 2) MRNs sent to hospitals in password-protected Excel files  Y  
(see [SOP DM005](#))

- 3) For primary data collection projects using laptops/USB key/mobile devices:
- Encryption software in place.  Y
  - 2 levels of unique passwords must comply with ICES password policy.  Y
  - Anonymization at collection point: collected under unique study number.  Y
  - Data collection tool complies with ICES standards for primary databases on laptops. (see Mobile Devices Policy)  Y

- 4) Are complete copies of reports / tests required?  Y  N  
If Yes:
- Limited numbers of reports may be scanned where abstraction difficult or untenable. Consult the Privacy Office.  Y
  - Paper reports / tests will be de-identified; assigned a unique number only and couriered to ICES.  Y

- 5) Append methods describing encryption methods and protections, if you plan to transmit data back to ICES.  Y

**D. PUBLIC BENEFIT**  
(Legislation requires completion of this section)

- 1) What is the public benefit of this Data use: (eg. Research that contributes to the effectiveness, quality, equity and efficiency of health care in Ontario) that are expected / anticipated from the project? Identify any potential impact.

This research is intended to improve the understanding of renal disease in pregnancy. Knowledge of trends, risk factors, outcomes as they relate to acute kidney injury in pregnancy will contribute to improved quality of care for pregnant women in Ontario.

**E. ESTIMATION OF HARM**  
(Legislation requires completion of this section)

**Note:** Cell sizes less than or equal to 5 cannot be reported without prior written approval from the President and CEO of ICES.

- 1) Please describe the level at which the results will be reported (e.g. level of individuals, institution or region – smallest units)

Aggregate data only.

- 2) Describe any reasonably foreseeable harms that may arise from the use of the data. Are there any ways this study might identify, stigmatize, or otherwise harm patients, practitioners or institution(s)? How will these reasonably foreseeable harms be addressed?

No foreseeable harms

**F. ALTERNATIVES**  
(Legislation requires completion of this section)

- 1) Is it possible to do this research without using personal health information?  Y  N
- 2) Were any alternative methods considered / rejected as less privacy-invasive for achieving the desired objectives? If so, please describe briefly (this provides a means of assessing any real / potential privacy-adverse impact which may be challenged by external sources).  Y  N

**G. TIMEFRAME, DATA RETENTION/DESTRUCTION**

- 1) What is the proposed time frame of the project:
- Anticipated start-up date: 01/06/2012 (dd/mm/yyyy)
  - Anticipated completion date: 01/06/2014 (dd/mm/yyyy)
- 2) Retention and disposal policies.  
Stipulate retention prior to dataset destruction period.  
Notification to PI to be sent on: 12/18 (mm/yy)
- Document shredding.  Y
  - Destruction of electronic media (magnetic and optical disks, cartridges, CDs).  Y
  - Dataset Destruction date: 01/06/2019 (dd/mm/yy):

### H. FINANCIAL INFORMATION

1) What is the funding source for this study?

**ICES – Core Budget \***

\* Do not use unless expenditures have been pre-approved and included in the ICES core budget.

- Ministry Workplan (MOHLTC)\*  Y
- ICES Funded (non-MOHLTC/non-grant)\*  Y

**Externally Funded**

- MOHLTC Program Funded (Special Projects)  Y
- CCO  Y
- Peer Reviewed Grant (Specify Source)   Y
- External Contract  Y
- MOHLTC Third Party Funded (MOHLTC funds held at another institution.)  Y
- Other funding source (Specify Source) Amit Garg Internal Research  Y  
Funds

2) **PAW:** Have you completed and submitted a Project Activation Worksheet?  Y

**NOTE: A project TRIM number will not be assigned unless the budget section of the PAW is completed.**

ICES Privacy Impact Assessment Form

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**I. ETHICS APPROVAL STATUS**

- Ethics approval sought by President and CEO and Chief Privacy Officer (anonymized data studies with administrative data)  Y
- Chart abstraction study – ethics approval obtained (append copies of REB approval)  Y
- Clinical study – ethics approval obtained (append copies of REB approval) (Include patient consent form *if applicable*)  Y

**J. COMPLIANCE WITH CORPORATE RULES FOR ALL STAFF**Is a data-sharing agreement required for this project?  Y  N

- If yes:
  - Has the Privacy Office and the Program Administrator been notified? **OR**  Y  N
  - Data sharing agreements have been signed.  Y  N
- Confidentiality agreements have been signed by ALL project staff.  Y
- All project participants have been familiarized with ALL ICES privacy and confidentiality policies and procedures.  Y
- Copies of proposal, Privacy Impact Assessment form and Project Activation Worksheets have been filed with the Program Administrator. Electronic copies of each of these have been sent to the ICES Privacy Office.  Y
- If external Ethics approval has been sought, append copy to documents  Y
- Cell sizes less than or equal to 5 cannot be reported (any exceptions must be approved in writing by ICES President and CEO).  Y
- Your interest in the disclosure of the data for your research purpose will not result in actual, perceived or potential conflict of interest with your other duties as researcher.  Y
- You have received and agree with ICES Media Relations Policy  Y
- You have read and agree with the ICES Conflict of Interest Policy  Y

**K. SOP'S AND POLICIES**

- You and your project team have reviewed all current Policies and SOP's applicable to this project  Y  N

If you selected "N" please find the up-to-date SOP's and Polices at the following locations:

- ICES Intranet – under "Policies and Forms"
- ICES Research Practice site
- For access to the documents, please contact your Program Administrator.
- For questions about a specific Policy or SOP, please contact the owner listed on the document.

\_\_\_\_\_  
Signature of Investigator / Scientist      Date (dd/mm/yy)

\_\_\_\_\_  
Signature of Scientific Program Leader      Date (dd/mm/yy)

\_\_\_\_\_  
Signature of Site Director, if applicable      Date (dd/mm/yy)

\_\_\_\_\_  
CEO Approval      Date (dd/mm/yy)

\_\_\_\_\_  
Privacy Office Approval      Date (dd/mm/yy)

**This section is for the use of Ontario Cancer Registry**

\_\_\_\_\_  
Signature      Date (dd/mm/yy)  
on behalf of  
 CCO  
 Cancer Research Program

**\*Reference:**

For more information, please refer to the *Personal Health Information Protection Act (PHIPA)* which is found at: [http://www.e-laws.gov.on.ca/html/statutes/english/elaws\\_statutes\\_04p03\\_e.htm](http://www.e-laws.gov.on.ca/html/statutes/english/elaws_statutes_04p03_e.htm)  
The Regulation to the Act (Reg. 329/04) can be found at: [http://www.e-laws.gov.on.ca/html/regis/english/elaws\\_regs\\_040329\\_e.htm](http://www.e-laws.gov.on.ca/html/regis/english/elaws_regs_040329_e.htm)



## Appendix D: Copyright Permission

From: Bonnie O'Brien [REDACTED]  
 Subject: RE: Permission to include published manuscript in Master's Thesis  
 Date: June 22, 2015 at 10:38 AM  
 To: Ainslie Hildebrand [REDACTED]

BO

Permission is granted.

Bonnie O'Brien  
 Managing Editor, JASN

Don't forget to register for ASN Kidney Week 2015, the premier nephrology meeting in the world: [www.asn-online.org/kidneyweek/](http://www.asn-online.org/kidneyweek/)

From: Ainslie Hildebrand [REDACTED]  
 Sent: Saturday, June 20, 2015 11:31 AM  
 To: [REDACTED]  
 Subject: Permission to include published manuscript in Master's Thesis

Hi there,

I recently had the following article published in JASN:  
 Hildebrand AM, Liu K, Shariff SZ, Ray JG, Sontrop JM, Clark WF, Hladunewich MA, Garg AX. Characteristics and outcomes of AKI treated with dialysis during pregnancy and the postpartum period. J Am Soc Nephrol. 2015 May 14. [Epub ahead of print]  
 Article D: JASN2014100954

This is the content of my Master's thesis and I would like permission to include a version of this manuscript as a chapter in my thesis.

How do I go about obtaining a letter of permission from the publisher?

Thanks,

Ainslie  
 —  
 Ainslie Hildebrand, MD, FRCPC  
 Nephrologist, Research Fellow  
 MSc Candidate, Clinical Epidemiology & Biostatistics  
 Western University  
 London, Ontario, Canada

Dear Author,

Thank you for using the Journal of the American Society of Nephrology Author Center to return your corrected article proof. Your corrected PDF and any additional material have been automatically submitted for processing with the following comments:

"One minor, but important, formatting edit to Table 2. Thanks!".

Your article information:

Article D: JASN2014100954  
 Article Title: Characteristics and Outcomes of AKI Treated with Dialysis during Pregnancy and the Postpartum Period

Regards,

Journal of the American Society of Nephrology  
 Production Specialist

03/03/15 1:29 PM >>>

Dear Dr. Hildebrand,

On behalf of Editor-in-Chief, Karl Nath, and Associate Editor, Dr. Phyllis August, I am pleased to inform you that your manuscript is now suitable for publication without further revision and will appear in the next available issue of the Journal of the American Society of Nephrology (JASN).

Regarding the NIH Public Access Policy: We will submit your final published article directly to PubMed Central, where it will be publicly accessible within 12 months of publication. This satisfies the NIH Public Access Policy; therefore, you do not need to submit the accepted manuscript yourself. If you have any questions about this policy, please do not hesitate to contact me.

Disclosure of Support: Authors are required to divulge any relationships with pharmaceutical firms or other entities (such as employment contracts, consultancy, advisory boards, speaker bureaus, membership of Board of Directors, stock ownership) that could be perceived to

## Curriculum Vitae

### PROFESSIONAL & ACADEMIC POSITIONS

- 2015-09-01 to present      **Assistant Professor, Department of Medicine, Division of Nephrology**  
The University of Alberta, Edmonton, AB
- 2015-09-01 to present      **Medical Director of the Glomerulonephritis Clinic, Division of Nephrology**  
The University of Alberta, Edmonton, AB

### EDUCATION & DEGREES

- 2011-09-06 to present      **Master of Science, Clinical Epidemiology and Biostatistics**  
Western University, London, ON
- 2003-08-25 to 2007-05-10      **Doctor of Medicine**  
The University of Manitoba, Winnipeg, MB
- 1999-09-01 to 2002-05-01      **Bachelor of Science**  
The University of Manitoba, Winnipeg, MB

### POSTGRADUATE MEDICAL EDUCATION

- 2014-07-01 to 2015-06-30      **Fellowship, Glomerulonephritis**  
The University of Toronto, Toronto, ON
- 2014-07-01 to 2015-06-30      **Fellowship, Renal Diseases of Pregnancy**  
The University of Toronto, Toronto, ON
- 2010-07-01 to 2012-06-30      **Fellowship, Nephrology**  
Western University, London, ON
- 2007-07-01 to 2010-06-30      **Residency, Internal Medicine**  
The University of Manitoba, Winnipeg, MB

### POST-DOCTORAL RESEARCH FELLOWSHIPS

- 2012-07-01 to 2015-06-30      **Clinical Investigator Program, \$200,000**  
*Accredited by the Royal College of Physicians and Surgeons of Canada*  
Western University, London, ON
- 2012-07-01 to 2013-06-30      **Ontario Drug Policy Research Network Student Training Program, \$40,000**  
Ontario Drug Policy Research Network, ON

### LICENSURE & BOARD CERTIFICATION

- 2015-06-26      College of Physicians and Surgeons of Alberta [025610]
- 2012-09-24      Fellow of the Royal College of Physicians and Surgeons of Canada (Nephrology)
- 2011-06-30      Fellow of the Royal College of Physicians and Surgeons of Canada (Internal Medicine)
- 2008-12-16      Licentiate of the Medical Council of Canada (Part I 2007, Part II 2008) [107440]

## HOSPITAL APPOINTMENTS

2015-09-01 to present      Consultant Nephrologist, University of Alberta Hospital, Edmonton, AB  
 2012-12-01 to 2015-08-30      Internal Medicine Hospitalist, Thunder Bay Regional Health Sciences Centre, Thunder Bay, ON (locum coverage)

## PROFESSIONAL SOCIETIES

2011 to present      Royal College of Physicians and Surgeons of Canada  
 2010 to present      Canadian Society of Nephrology (CSN)  
 2010 to present      American Society of Nephrology (ASN)

## HONORS & AWARDS

2013-02-01      **Young Investigators' Forum Finalist (\$500)**, Montreal, QC: Adherence to prescribing recommendations made on a provincial formulary  
 2012-05-01      **Best Published Paper Derived from Resident Research Day (\$500)**, University of Manitoba, Department of Medicine, Winnipeg, MB: Peritonitis and exit site infections in First Nations patients on peritoneal dialysis  
 2010-05-01      **2<sup>nd</sup> Prize for Clinical Investigation Podium Presentation (\$200)**, University of Manitoba, Department of Medicine, Winnipeg, MB: Peritonitis and exit site infections in First Nations patients on peritoneal dialysis  
 2011-09-01      **Schulich Graduate Scholarship**, Department of Epidemiology and Biostatistics, Western University  
 2009-05-01      **2<sup>nd</sup> Prize for Clinical Investigation Research Poster (\$200)**, University of Manitoba, Department of Medicine, Winnipeg, MB: Creating a model for improved chronic kidney disease care: designing parameters in quality, efficiency and accountability  
 2008-05-01      **2<sup>nd</sup> Prize for Case Report Research Poster (\$200)**, University of Manitoba, Department of Medicine, Winnipeg, MB: Myocardial siderosis due to hemochromatosis in an individual with hypertrophic cardiomyopathy  
 2000-05-01      **Merck Index Award**, University of Manitoba, Department of Chemistry  
 1999-08-01      **University of Manitoba Entrance Scholarship**, University of Manitoba, August 1999

## INVITED PRESENTATIONS (NATIONAL)

2016-05-14      *Literature review series for the busy clinician - update on diagnostics and treatment of glomerular disease.* Canadian Society of Nephrology Meeting, Halifax, NS  
 2012-05-01      *Peritonitis and exit site infections in First Nations patients on peritoneal dialysis.* University of Manitoba Resident Research Day, Winnipeg, MB

## RESEARCH GRANTS

2016-09-30 to 2017-03-30      **TTP Foundation**  
 Title: Long-term vascular outcomes of idiopathic thrombotic microangiopathy treated with plasma exchange  
 Role: Principal and Project Lead (Co-PI Dr. William Clark)  
 Total Budget: \$65,517

- 2016-01-01 to 2018-12-31      **AMGEN Canada**  
 Title: Creating a model for improved glomerulonephritis care in Northern Alberta  
 Role: Principal Investigator  
 Total Budget: \$600,000
- 2014-07-01 to 2016-06-30      **Kidney Foundation of Canada (co-funded with TTP Foundation)**  
 Title: Long-term vascular outcomes of idiopathic thrombotic microangiopathy treated with plasma exchange  
 Role: Co-Investigator and Project Lead (PI Dr. William Clark)  
 Total Budget: \$99,720

## PEER-REVIEWED PUBLICATIONS

1. Roshanov PS, Walsh M, Devereaux PJ, MacNeil SD, Lam NN, **Hildebrand AM**, Acedillo RR, Mrkobrada M, Chow CK, Lee VW, Thabane L, Garg AX. External validation of the Revised Cardiac Risk Index and update of its renal variable to predict 30-day risk of major cardiac complications after noncardiac surgery: rationale and plan for analyses of the VISION study. *BMJ Open* 2016 (In Press)
2. **Hildebrand AM**, Hladunewich MA, Garg AX. Preeclampsia and the Long-term Risk of Kidney Failure. *Am. J. Kidney Dis.* 2016 (In Press)
3. Clark WF, Huang SH, Walsh M, Farah M, **Hildebrand AM**, Sontrop JM. Plasmapheresis for the treatment of kidney diseases. *Kidney Int.* 90(5): 974-984, 2016
4. Thejeel B, Garg AX, Clark WF, Liu AR, Iansavichus AV, **Hildebrand AM**. Long-term outcomes of thrombotic microangiopathy treated with plasma exchange: A systematic review. *Am. J. Hematol.* 91(6): 623-30, 2016
5. **Hildebrand AM**, Liu K, Shariff SZ, Ray JG, Sontrop JM, Clark WF, Hladunewich MA, Garg AX. Characteristics and outcomes of AKI treated with dialysis during pregnancy and the postpartum period. *J. Am. Soc. Nephrol.* 26(12): 3085-91, 2015
6. Garg AX, Nevis IF, McArthur E, Sontrop JM, Koval JJ, Lam NN, **Hildebrand AM**, Reese PP, Storsley L, Gill JS, Segev DL, Habbous S, Bugeja A, Knoll GA, Dipchand C, Monroy-Cuadros M, Lentine KL; Donor Nephrectomy Outcomes Research (DONOR) Network. Gestational Hypertension and Preeclampsia in Living Kidney Donors. *N. Engl. J. Med.* 372(2): 124-33, 2015
7. Iansavichus AV, **Hildebrand AM**, Haynes RB, Wilczynski NL, Levin A, Hemmelgarn BR, Tu K, Nesrallah GE, Nash DM, Garg AX. High-performance information search filters for chronic kidney disease content in PubMed, Ovid Medline and Embase. *Am. J. Kidney Dis.* 65(1): 26-32, 2015
8. Farah M, **Hildebrand AM**, Huang S, Dammas H, Clark WF. Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome in 2014: Current Knowledge and Outcomes with Plasma Exchange. *Oncology & Hematology Review* 10(2): 82-9, 2014
9. **Hildebrand AM**, Yao Z, Gomes T, Camacho X, Garg AX, Juurlink DN, Mamdani MM, Dhalla IA. Adherence to prescribing recommendations made on a provincial formulary. *Healthcare Policy* 9(4): 20-30, 2014
10. Garg AX, Vincent J, Cuerden M, Parikh C, Devereaux PJ, Teoh K, Yusuf S, **Hildebrand A**, Lamy A, Zuo Y, Sessler DI, Shah P, Abbasi SH, Quantz M, Yared JP, Noiseux N, Tagarakis G, Rochon A, Pogue J, Walsh M, Chan MT, Lamontagne F, Salehiomran A, Whitlock R; SIRS Investigators. Steroids In caRdiac Surgery (SIRS) trial: acute kidney injury substudy protocol of an international randomised controlled trial. *BMJ Open* 4(3): e004842, 2014
11. **Hildebrand AM**, Huang S, Clark WF. Plasma Exchange for Renal Disease: What is the Best Evidence? *Adv. Chronic Kidney Dis.* 21(2): 217-27, 2014
12. Botto et al. on behalf of the VISION Study Investigators (**Hildebrand A** an investigator). Myocardial Injury after Noncardiac Surgery: A Large, International, Prospective Cohort Study

- Establishing Diagnostic Criteria, Characteristics, Predictors, and 30-day Outcomes. *Anesthesiology* 120(3): 564-78, 2014
13. **Hildebrand AM**, Iansavichus AV, Haynes RB, Wilczynski NL, Mehta RL, Parikh CR, Garg AX. High Performance Information Search Filters for Acute Kidney Injury Content in PubMed, Ovid Medline, and Embase. *Nephrol. Dial. Transplant* 29(4): 823-32, 2014
  14. **Hildebrand AM**, Garg AX. Blood pressure targets in chronic kidney disease: does proteinuria dictate how low we go? *CMAJ* 185(11): 941-2, 2013
  15. **Hildebrand AM**, Iansavichus AV, Lee CW, Haynes RB, Wilczynski NL, McKibbin A, Hladunewich MA, Clark WF, Cattran DC, Garg AX. Glomerular disease search filters for Pubmed, Ovid Medline, and Embase: a development and validation study. *Med. Inform. Decis. Mak.* 12(1): 49, 2012
  16. Clark WF, **Hildebrand A**. Attending rounds: microangiopathic hemolytic anemia with renal insufficiency. *Clin. J. Am. Soc. Nephrol.* 7:342–47, 2012
  17. Huang S, **Hildebrand AM**, Clark WF. Brief review: management of lupus nephritis – randomized controlled trials: an update. *OJIM* 1(02): 25–31, 2011
  18. **Hildebrand A**, Komenda P, Miller L, Rigatto C, Verrelli M, Sood AR, Sathianathan C, Reslerova M, Eng L, Eng A, Sood M. Peritonitis and exit site infections in First Nations patients on peritoneal dialysis. *Clin. J. Am. Soc. Nephrol.* 5(11): 1988-95, 2010
  19. Collister D, Rigatto C, **Hildebrand A**, Mulchey K, Palmondon J, Sood MM, Reslerova M, Arsenio J, Coudiere R, Komenda P. Creating a model for improved chronic kidney disease care: designing parameters in quality, efficiency and accountability. *Nephrol. Dial. Transplant* 25(11): 3623-30, 2010
  20. **Hildebrand AM**, Bhagirath KM, Ariyaratnam V, Walker JR, Houston DS, Zieroth S, Tam JW, Kirkpatrick I, Jassal DS. Myocardial siderosis due to hemochromatosis in an individual with hypertrophic cardiomyopathy. *Can. J. Cardiol.* 25(12): e424-5, 2009

## ABSTRACTS

1. Thejeel B, Garg AX, Clark WF, Liu AR, Iansavichus AV, **Hildebrand AM**. Long-term outcomes of thrombotic microangiopathy treated with plasma exchange: A systematic review. *American Society of Nephrology* 2015 [POSTER]
2. **Hildebrand AM**, Liu K, Shariff SZ, Ray JG, Sontrop JM, Clark WF, Hladunewich MA, Garg AX. Characteristics and outcomes of AKI treated with dialysis during pregnancy and the postpartum period. *Canadian Society of Nephrology* 2014 [POSTER]
3. **Hildebrand AM**, Huang S, Clark WF. Plasma Exchange for Renal Disease: What is the Best Evidence? *Canadian Society of Nephrology* 2014 [POSTER]
4. **Hildebrand AM**, Liu K, Shariff SZ, Ray JG, Sontrop JM, Clark WF, Hladunewich MA, Garg AX. Characteristics and outcomes of AKI treated with dialysis during pregnancy and the postpartum period. *American Society of Nephrology* 2013 [POSTER]
5. **Hildebrand AM**, Iansavichus AV, Haynes RB, Wilczynski NL, Mehta RL, Parikh CR, Garg AX. High Performance Information Search Filters for Acute Kidney Injury Content in PubMed, Ovid Medline, and Embase. *American Society of Nephrology* 2013 [POSTER]
6. **Hildebrand AM**, Yao Z, Gomes T, Camacho X, Garg AX, Juurlink DN, Mamdani MM, Dhalla IA. Adherence to prescribing recommendations made on a provincial formulary. *Canadian Society of Nephrology* 2013 [POSTER]
7. **Hildebrand A**, Komenda P, Miller L, Rigatto C, Verrelli M, Sood AR, Sathianathan C, Reslerova M, Eng L, Eng A, Sood M. Peritonitis and exit site infections in First Nations patients on peritoneal dialysis. *American Society of Nephrology* 2010 [POSTER]

8. **Hildebrand A**, Komenda P, Miller L, Rigatto C, Verrelli M, Sood AR, Sathianathan C, Reslerova M, Eng L, Eng A, Sood M. Peritonitis and exit site infections in First Nations patients on peritoneal dialysis. *Canadian Society of Nephrology* 2010 [POSTER]
9. Collister D, Rigatto C, **Hildebrand A**, Mulchey K, Palmondon J, Sood MM, Reslerova M, Arsenio J, Coudiere R, Komenda P. Creating a model for improved chronic kidney disease care: designing parameters in quality, efficiency and accountability. *Canadian Society of Nephrology* 2009 [POSTER]

## MEDIA INTERVIEWS

- |            |   |
|------------|---|
| 2016-02-01 | Alberta Health Services Edmonton Zone News, Glomerulonephritis Clinic feature ( <a href="http://www.albertahealthservices.ca/assets/zone/ahs-zone-print-edmonton-2016-02.pdf">http://www.albertahealthservices.ca/assets/zone/ahs-zone-print-edmonton-2016-02.pdf</a> )                           |
| 2015-12-16 | Edmonton Journal, Glomerulonephritis Clinic feature ( <a href="http://edmontonjournal.com/news/local-news/new-clinic-at-university-of-alberta-hospital-helps-kidney-patients">http://edmontonjournal.com/news/local-news/new-clinic-at-university-of-alberta-hospital-helps-kidney-patients</a> ) |
| 2015-12-16 | Global TV News, Glomerulonephritis Clinic feature ( <a href="http://globalnews.ca/tag/edmonton-health-matters">http://globalnews.ca/tag/edmonton-health-matters</a> )   |
| 2015-12-16 | CBC News, Glomerulonephritis Clinic feature (link not available)  |
| 2015-12-16 | CTV News, Glomerulonephritis Clinic feature (link not available)  |

## RESEARCH COLLABORATION

### *Research Studies*

- |                |   |
|----------------|---|
| 2016 – present | <b>Site Co-Investigator</b> , Canadian Institutes of Health Research’s Strategy for Patient-Oriented Research (SPOR): Canadians Seeking Solutions and Innovations to Overcome Chronic Kidney Disease (Can-SOLVE CKD), Glomerulonephritis Translational Research Program |
| 2016 – present | <b>Site Co-Investigator</b> , Abatacept for the Treatment of Relapsing, Non-Severe, Granulomatosis With Polyangiitis (Wegener’s), NCT02108860   |
| 2016 – present | <b>Site Co-Investigator</b> , Therapeutic Evaluation of Steroids in IgA Nephropathy Global Study (TESTING Study), NCT01560052   |

### *Research Groups*

- |                |   |
|----------------|---|
| 2016 – present | <b>Member</b> , Canadian Network for Research on Vasculitides (CanVasc)                                       |
| 2015 – present | <b>Member</b> , Alberta Kidney Disease Network (AKDN)   |
| 2012 – present | <b>Member</b> , Institute for Clinical Evaluative Sciences (ICES) Kidney Dialysis and Transplantation Program |