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RISK OF HYPERTENSIVE DISORDERS IN PREGNANCY OF LIVING KIDNEY DONORS: A PILOT COHORT STUDY

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RISK OF HYPERTENSIVE DISORDERS IN PREGNANCY OF LIVING KIDNEY DONORS: A PILOT COHORT STUDY

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ABSTRACT AND KEYWORDS

The majority of living kidney donors is women. Female donors often ask their physicians whether donation will have any effect on their future pregnancies. Previous studies conclude that living donation poses no great harm for women who wish to become pregnant after donation. In Ontario, we are able to study this issue using large health care databases, and data from the Trillium Gift of Life Network. In this pilot study, hypertensive disorders of pregnancy (gestational hypertension, preeclampsia, eclampsia) were compared among kidney donors and healthy women who did not become kidney donors. 55 donors were studied who became pregnant following kidney donation comparing them to 502 matched female controls. Controls were matched on age, income, date of child birth, date of last pregnancy, history of previous pregnancy with hypertensive complications, and current multiple gestations. There was no statistically significant difference in the risk of hypertensive disorders of pregnancy between donors and controls (13% vs. 8%; OR 1.78; 95% CI 0.75 to 4.19; p-value=0.19). However, the wide confidence interval and small sample size leaves uncertainty on any conclusions to be drawn. The results of this pilot study provide the foundation for a more definitive study, to rule out a smaller yet clinically important risk.

Keywords:
administrative database, cohort study, eclampsia, gestational hypertension, intrauterine growth retardation, living kidney donation, low birth weight, preeclampsia, pregnancy, preterm birth.

DEDICATION

To my parents,

for instilling in me the spirit of obligation to education.

To my husband,

Arun

his love and support helped me to pursue my dreams.

I owe him my every success.

□□□□□

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LIST OF ABBREVIATIONS, SYMBOLS AND NOMENCLATURE

95% CI: 95% confidence interval

20-HETE: 20-Hydroxyeicosatetraenoic Acid

ACP Journal Club: American College of Physicians Journal Club

BP: blood pressure

CCI: Canadian Classification of Health Interventions

CCP: Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures

CIHI: Canadian Institute for Health Information

CIHR: Canadian Institutes of Health Research

DARE: Database of Abstracts of Reviews of Effects

Dx: diagnostic

GFR: Glomerular Filtration Rate

HDP: hypertensive disorders of pregnancy

ICD: International Classification of Diseases

ICD 9: International Classification of Disease, Ninth Revision

ICD 9 CM: International Classification of Disease, Ninth Revision, Clinical Modification

ICD 10: International Classification of Diseases and Related Health Problems, Tenth Revision

ICES: Institute for Clinical Evaluative Sciences

IUGR: Intra-Uterine Growth Retardation

LBW: Low birth weight

ODD: Ontario Diabetes Database

OHIP: Ontario Health Insurance Plan

RPF: renal plasma flow

SES: socioeconomic status

SGA: Small for Gestational Age

TGLN: Trillium Gift of Life Network

VEGF: Vascular Endothelin Growth Factor

WHO: World Health Organization

CHAPTER 1- INTRODUCTION

1.1. Living Kidney Donation: "The Gift of Life"

Transplantation is the preferred treatment option for patients with kidney failure (1). Compared to dialysis, patients who receive a transplant have a 70% reduction in the risk of death, a dramatically improved quality of life, and reduced health care costs (2-4). Living kidney donation has many advantages over deceased donation. Prolonged waiting times are reduced and transplantation can take place when the donor and recipient are in the best possible health.

However, there are now over 2,800 Canadians on the waiting list for a kidney (5). Currently, in 2009, there are 1194 people in Ontario on a waiting list for a kidney. The average wait time in Ontario can be 4 to 8 years, depending on various factors particularly, the recipient's blood type (6). To meet demand, rates of living kidney donation have nearly doubled over the last decade and continue to rise (7;8). Approximately 27,000 living kidney donations take place around the world each year (9). In Canada, the number of living donors surpassed the number of deceased donors in the year 2001, and the gap is widening.

Giving the gift of improved health to another person can be a very positive experience. However, the altruistic act of living kidney donation remains a complex medical, psychosocial and financial issue. Even after five decades of practice, the implications of living donation on maternal and fetal outcomes remain uncertain. To optimize the practice, any adverse outcomes of living donation need to be carefully understood and minimized. There is now global consensus that we need better estimates of any maternal and fetal outcomes on donor risks (10;11).

1.1.1. Most Donors are Women

Studies confirm that women constitute the majority of living kidney donors (12). Several factors may explain this phenomenon. Living kidney donation previously used to take place only among biologically related donors. But recently, biologically unrelated donors, like spouses also donate. Studies report that there is a predominance of women among spousal donors. The United Network for Organ Sharing in the United States, reported that

73% of the 360 spousal donations were from wife to husband (12). Men are found to have more kidney failure compared to women. A study from the United States concluded that women are more likely to donate a kidney than men (RR: 1.28; $P < 0.001$) (13). This may be partly attributed to the increase in the number of males having kidney failure compared to women (14). Finally, compared to men, women were more likely to perceive donation as an extension of their family obligation (12).

1.2. Conclusions at the International Consensus Conference

One of the main concerns of female living kidney donors is the impact of kidney donation on their ability to have children. At the 2003 Amsterdam international consensus conference, it was concluded that:

> Donor nephrectomy is not detrimental to the prenatal course or outcome of future pregnancies. There are no data to suggest that hyperfiltration associated with the combination of unilateral nephrectomy and pregnancy leads to significant hypertension, proteinuria, change in glomerular filtration, or abnormalities of urinary sediment. It is recommended, however, to delay pregnancy until at least 2 months after nephrectomy to assess renal compensation prior to conceptions with evaluation including blood pressure, glomerular filtration rate (GFR), and assessment for microalbuminuria. This emphasis is to verify that postpartum renal function is normal (15).

However, this recommendation is based on little evidence.

1.3. Living with One Kidney and Subsequent Hypertension: Non-Pregnant Individuals

The complex, codependent relationships between kidney function and hypertension outside of pregnancy are well recognized. For this reason, the risk of hypertension after kidney donation has been frequently investigated; some, but not all studies identify an increase in hypertension risk after donation (16). A comprehensive review of 48 studies examining changes in blood pressure after kidney donation (from 28 countries following a total of 5145 donors) was published in 2006. The results of the meta-analysis show that blood pressure was 5mmHg higher in donors than in non-donor controls (16).

1.4. Incidence of Hypertensive Disorders of Pregnancy

A systolic blood pressure ≥ 140 mm Hg and a diastolic blood pressure of ≥ 90 mm Hg define hypertension in pregnancy. In general, it is well known that high blood pressures are found in 5-10% of all pregnancies. Preeclampsia, which is high blood pressure with proteinuria, is the primary cause of maternal death in many countries and is responsible for 20-25% of perinatal mortality (17). The incidence of preeclampsia is 3-5% in nulliparous and 0.5% in multiparous women (17). Nullipara is a woman who has never been previously pregnant, whereas multipara is a woman who has previously given birth to at least one child.

A potential link between the act of kidney donation and child-bearing lies in the outcome of hypertension. Hypertensive disorders of pregnancy (HDP) are classified into chronic (preexisting) hypertension, gestational hypertension, preeclampsia, eclampsia and preeclampsia superimposed on preexisting hypertension.

It is to be noted that there are variations in the nomenclature used to refer to the same condition. This thesis focuses on gestational hypertension, preeclampsia and eclampsia, as defined by the World Health Organization (WHO).

Knowledge of expected outcomes in the non-donor general population helps inform an understanding of potential risks to the living donor. As seen in Table 1, nine well conducted prospective studies on the incidence of hypertensive disorder of pregnancy (HDP) were selected to derive an estimate. The nine studies were conducted in Canada, USA, Norway, Finland and Netherlands. The sample size ranged from 751 to 371,021 pregnancies. The years of recruitment ranged from 1979-2006. The overall incidence rate of hypertensive disorder of pregnancy was estimated to be about 10% in well characterized general population cohorts (Table 1). The incidence of gestational hypertension ranged from 4.4% to 11%, preeclampsia 1.9% to 5.9%, and eclampsia less than 0.1%. The weighted average incidence of gestational hypertension is 7.9%, preeclampsia is 3.3%, and eclampsia is 0.06%.

Table 1: Studies from the general population on the incidence of hypertensive disorders in pregnancy

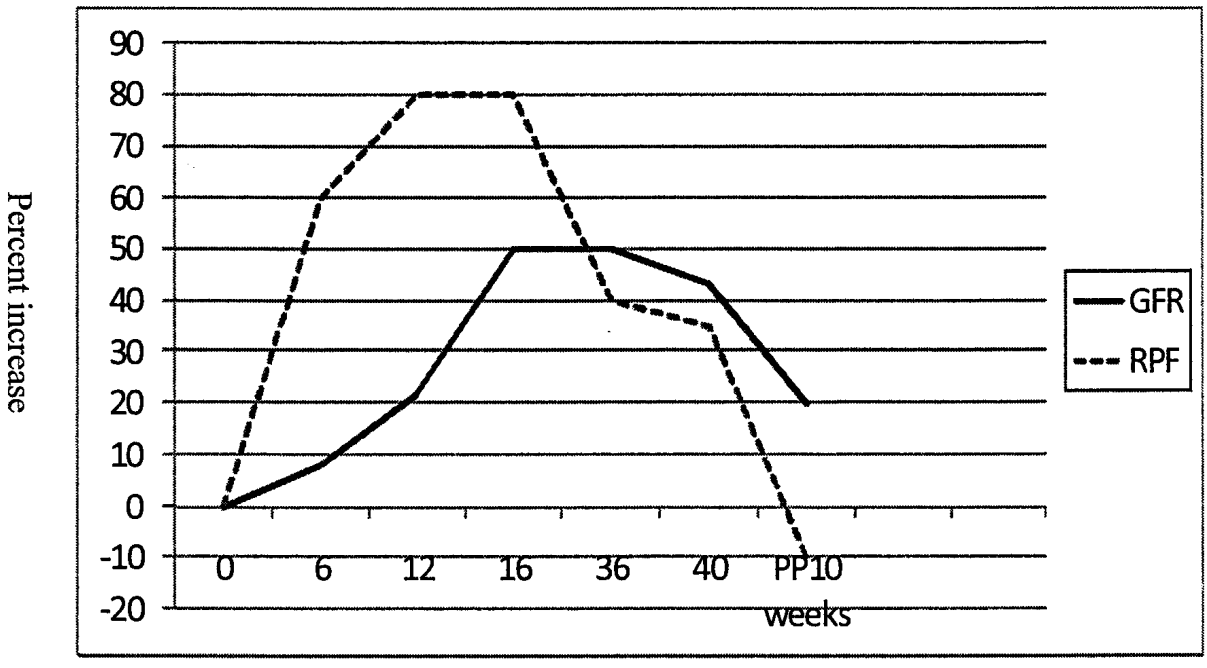
Study, Year†	Primary Location	N	Years of recruit-ment	Incidence of gesta-tional hyper-tension[1] %	Incidence of preeclamp-sia[2] %	Incidence of eclamp-sia[3] %	Mean Age	Nulli /Primi-parous* %	Multi-parous* %
Moutquin JM 1990 (18)	Montreal, Canada	751	1979-1984	(...)	5.9	(...)	25.5 (4.4)	100	0
Bodnar LM 2005 (19)	Pittsburg, USA	1179	1997-2001	(...)	4.9†	(...)	(...)	100	0
Ness RB 2003¶ (20)	Pittsburg, USA	2211	1997-2001	(...)	3.8†	(...)	(...)	57	43
Wolf M 2004 (21)	Massachu-setts, USA	3244	1998-2002	6.6	3.8*	(...)	26.3 (5.3)	100	0
Clausen T 2006 (22)‡	Oslo, Norway	3677	1995-1997	4.8	2.5	(...)	29.8 (4.6)	51	49
Vollebregt KC 2008 (23)	Amsterdam, Netherlands	3679	2003-2004	4.4	3.5*	(...)	29.9 (5.1)	100	0
Hartikainen AL, 1998 (24)	Oulu, Finland	9247	1985-1986	11.0	1.9	(...)	(...)	34	66
BodnarLM 2006 (25)	Pittsburg, USA	38,188	1958-1964	(...)	3.6	(...)	(...)	31	69
Zwart JJ 2008 (26)	Leiden, Netherlands	371,021	2004-2006	(...)	(...)	0.06	(...)	48	52
	Weighted Average			7.9	3.3	0.06			

(...) Ellipses denote data not reported in the study.
†Studies arranged by sample size.
¶Loss to follow-up was reported as 5.5% and ‡ 6.4%
[1]Gestational hypertension, formerly known as pregnancy-induced hypertension or PIH, defined as new onset hypertension after 20 weeks gestation (≥ 140 mm Hg systolic *or* ≥ 90 mm Hg diastolic of two elevated blood pressure measurements 6 hours apart).
[2] Preeclampsia defined as gestational hypertension plus proteinuria (defined as > 0.3 g / 24 hours or two readings of 1+ proteinuria on dipstick at least 6 hours apart).
†Proteinuria defined as excretion of >300 mg of protein in 24 hours, a random sample of 2+, a catheterized sample of 1+, or a protein-creatinine ratio >0.3
*Proteinuria defined as ≥2+ by dipstick or ≥300 mg/24 h in the absence of urinary infection.
[3] Eclampsia defined as new onset of grand mal seizures in a woman with preeclampsia.
*Nullipara is a woman who has never been previously pregnant, primipara is a woman who may have been pregnant before but has never carried a pregnancy older than 20 weeks gestation, multipara is a woman who has previously given birth to at least one child.

1.5. The Kidney and Reproductive Health: Biological Considerations

The basis for the close interrelationship between reproductive function and renal function is intriguing and suggests that intact renal function is necessary for the physiologic adjustments to pregnancy, such as vasodilatation, lower blood pressure, increased plasma volume, and increased cardiac output. While hypertensive disorders of pregnancy are multifactorial in nature, the kidneys are inextricably linked (27). The kidneys are key regulators of salt and water, and pregnancy is a time of net salt and water retention. Over the whole period of gestation, there is retention of about 7.5L of water and 900 mmol of sodium (28). During normal pregnancy, glomerular filtration rate and renal plasma flow begin to increase progressively during the first trimester. By term, there is a 50%

Figure 1: Physiologic changes during normal pregnancy



GFR: Glomerular filtration rate, RPF: Renal plasma flow, PP: Postpartum pregnancy

increase in glomerular filtration rate (GFR) associated with single nephron hyperfiltration, a 50-80% increase in renal plasma flow and a decrease in blood pressure (Figure 1) (29). This parallels the increase in blood volume and cardiac output during pregnancy.

After donor nephrectomy, the GFR of the remaining kidney increases by 40%, and its response to hormones such as angiotensin II is altered (30). These alterations in vascular function could lead to higher blood pressure during pregnancy (31-35). Higher rates of hypertensive disorders of pregnancy are observed in those with advanced kidney disease (27).

Pregnancy outcomes after unilateral nephrectomy have been studied using animal models. Studies have demonstrated that reduced nephron mass is related to an increase in blood pressure and protein excretion in late pregnancy (36-39). An imbalance between the production of vasoconstrictor and vasodilatory products has long been deemed important in the development of preeclampsia (40). In mice, uninephrectomy and pregnancy served as additive stimuli for renal hypertrophy which was dependent on Vascular Endothelin Growth Factor (VEGF) (41;42). In rats, an increased risk of gestational hypertension and preeclampsia after unilateral nephrectomy was due to increased renal reactivity to angiotensin II involving 20-Hydroxyeicosatetraenoic Acid (20-HETE) (43).

In addition, human studies of living kidney donors depict higher serum uric acid and homocysteine levels after donation (44). These factors may also increase the risk of hypertensive disorders during pregnancy (45-47).

On this basis, is it possible that donating a kidney increases a woman's risk of hypertensive disorder of pregnancy (HDP)? Does a nephrectomy, through or outside the mechanism of HDP, predispose a donor to adverse fetal and maternal outcomes?

CHAPTER 2- LITERATURE REVIEW

2.1. Finding Relevant Articles

The objective of the literature review was to collect existing evidence on hypertensive complications in pregnancies of living kidney donors, and then to synthesize the results of the available literature. This would give a broad overview of all the studies done on this topic to date. Though only a few studies were identified, it is now recognized that there is growing interest on the effect of kidney donation on childbearing.

A large number of databases including Medline, PreMedline, Experta Medica, Cochrane database of systematic reviews, American College of Physicians Journal Club (ACP Journal club), Database of Abstracts of Reviews of Effectiveness (DARE), Cochrane Controlled Trials Register, Biosis Previews, the ISI Science Citation Index Expanded, Google Scholar, Elsevier's scientific search engine SCIRUS, clinicaltrials.gov, Cochrane Renal Group's Renal Trials Register, CiNii (Japan), and SCOPUS bibliographic databases, from the start date of each source to December 2008 were searched.

The search strategy was modified for each database and included the following terms as combinations of descriptors, subject headings and keywords: eclampsia, end stage renal failure, fetal outcomes, gestational hypertension, hypertension, hypertensive disorders of pregnancy, kidney donors, live births, living kidney donation, maternal outcomes, neonatal death, pregnancy, preeclampsia, and still births.

The reference lists of all relevant articles and reviews were screened. Cross-reference searches were performed of Internet and citation tracking using SCOPUS and ISI Science Citation Index, and using related articles featured in PubMed, OVID, Elsevier's SCIRUS and Google Scholar. Conference proceeding abstracts were also reviewed. All citations were downloaded into Reference Manager, version 11.0 (Thomson ISI Research-Soft, Philadelphia, PA).

2.2. Uncertainty in the Pregnancy Outcomes of Living Kidney Donors: Clinical Studies

The pregnancy outcomes of living kidney donors are described in five publications (48-52). Four studies are from the United States and another from Norway. The criteria of Hayden et al (53) was used to critically appraise the methods of each of these studies (studies summarized in Table 2).

The first study by Buszta et al. in 1985 (48) was a single centre retrospective chart review of 23 female kidney donors with 38 pregnancies. This study was conducted in the Cleveland Clinic foundation, USA, between 1963 and 1984. The results suggested women have normal pregnancies after kidney donation. Time to first conception after donation ranged from 3 months to 9 years. There was no mention of hypertensive disorders of pregnancy in any donor. Two of the donors (2/23) had 1+ proteinuria during pregnancy which resolved after child birth, another seven donors (7/23) had trace proteinuria. Six of the 37 pregnancies ended up in miscarriages and there were 32 viable births which included a set of twins. One pregnancy was counted as two for a set of twins in the study. The woman who was pregnant and had not yet delivered was not counted in the outcome of miscarriage. Of the 23 donors who delivered, 13 later had renal function tests 2 to 14 years after donation. At this assessment mean iothalamate assessment of GFR was 82 (SD 8) mL/min per 1.7 m (n=13), mean systolic blood pressure was 117 mmHg (SD 10), mean diastolic blood pressure was 72 mmHg (SD 9) and there was no evidence of proteinuria. Thus the authors concluded that hyperfiltration associated with the combination of unilateral nephrectomy and pregnancy did not lead to chronic sequelae and that blood pressure, glomerular filtration rate and urine protein levels remained normal.

The second study by Jones et al. was published in 1993 (50). The study followed 14 women with 25 pregnancies, at the University of Minnesota, USA from 1973 to 1992. Data on maternal and fetal outcomes were collected using a telephone survey. The mean time of first conception after donation was 3.3 years (range 0.3 to 10). The conclusions of the study were concordant with the results of Buszta et al. There were no events of gestational hypertension, preeclampsia or eclampsia reported during pregnancy. Except for two miscarriages other pregnancies ended in viable birth (23/25). However, two women

who had miscarriages went on to have normal pregnancies later. The study concluded kidney donation poses no increased risk of complications during pregnancy or renal impairment.

The third study by Wrenshall et al. was published in 1996 (52). In the study, surveys were sent to 220 female living kidney donors. Out of 220 women, 144 responded (response rate 65%), of whom 33 became pregnant after donation with 45 pregnancies. The primary centre for this study was the University of Minnesota, USA between the years 1985- 1992. They reported two pregnancies with gestational hypertension (4.4%) and preeclampsia (4.4%). Gestational hypertension in this study was defined as transient hypertension without proteinuria. Proteinuria was diagnosed in two of the 45 pregnancies (4.4%); however, there was no mention of the degree of proteinuria. There were six miscarriages (13.3%), one tubal pregnancy (2.2%) and four pregnancies which required preterm hospitalization (10.2%). There is a concern that some of these donors may have been described in Jones et al, 1993. Conclusively, this study reported that none of the complications of pregnancy exceeded the rate expected in the general population.

The fourth study by Reisaeter et al. published in 2008 compared women who had pregnancies before and after donation to women in the general population (51). Data from the Norwegian birth registry from 1967 to 2002 were reviewed. They described 326 women with 726 pregnancies: 620 pregnancies before donation (group 1) and 106 pregnancies after donation (group 2). A random sample of 21,511 pregnancies was obtained from the Norwegian registry to constitute the control group (group 3). They looked for both maternal and fetal outcomes including gestational hypertension, preeclampsia, eclampsia, low birth weight, stillbirths, preterm birth and neonatal deaths. Gestational hypertension was defined as new onset blood pressure $\geq$140/90 mmHg after 20 weeks of gestation or an increase in diastolic blood pressure of at least 15 mmHg or systolic blood pressure of at least 30 mmHg from the woman's average blood pressure before 20 weeks of gestation, without proteinuria. With proteinuria in this setting it was defined as preeclampsia. Proteinuria was defined as excretion of $\geq$0.3 g per day, usually equivalent to $\geq$1+ on a standard urine test strip. Birth weight was measured immediately after birth of the fetus. Low birth weight was $\leq$ 2500g. A fetus was recorded as still born if it died before or dur-

ing labour. A fetus born before 37 weeks of gestation was defined as a preterm birth. Gestational age was based on last menstrual period. Neonatal death was defined as fetal death less than 28 days after birth. The mean time from donation to delivery was 5 (±3.4) years; mean age at delivery for donors was 31.9 (±4.8) years and 28/106 (27.2%) were primiparous pregnancies after donation. Pregnancies were the unit of analysis, and examined as independent events. Correlation within women was not accounted for in the analysis. Also, compared to control pregnancies, pregnancies after donation were more likely to occur in older women who had previously given birth; reviewing counts on their own ignore important factors influencing the development of hypertensive complications of pregnancy. Notwithstanding these considerations, the diagnosis of preeclampsia was significantly more common in pregnancies after donation (5.7%), than before donation (2.6%) and among controls (3.1%). In pregnancies after donation, gestational hypertension was found to be in three (2.8%) pregnancies, low birth weight in nine (6.4%) pregnancies, stillbirths in three (2.8%) pregnancies, and there were 11 preterm births (10.8%). There were no incidences of eclampsia or neonatal birth. It is of interest to note that of the 106 pregnancies after donation, 28 (27.2%) were primiparous. One donor with chronic hypertension, defined as blood pressure of ≥140/90 mmHg prior to pregnancy or gestational week 20, was included among the pregnancies after donation.

Table 2: Studies of pregnancy in living kidney donors

Study	Pregnancies after donation	Setting (Years of Donation)	Study methods	Time to first conception after donation mean (range) years	Maternal and Fetal Outcomes
Buszta et al 1985[a] (48)	38 pregnancies in 23 donors	Cleveland Clinic Foundation, USA (1963-1984)	A review of prenatal and delivery records	...(0.03- 9)	no events of gestational hypertension, pre-eclampsia or eclampsia were described in any pregnancy 1+ proteinuria* in 2/23 (9%) donors (resolved after pregnancy) trace proteinuria* in 7/23 (30%) donors miscarriages*6/37 (16.2%) pregnancies 32 viable births* (1 set of twins)
Jones et al 1993 (50)	25 pregnancies in 14 donors	University of Minnesota, USA (1973-1992)	Telephone survey of donors about past pregnancies	3.3 (0.3-10)	no events of gestational hypertension, pre-eclampsia or eclampsia were described in any pregnancy miscarriages* 2/25 (8%) pregnancies 23 viable births*
Wrenshall et al 1996 (52)	45 pregnancies in 33 donors	University of Minnesota, USA (1985-1992)	Mailed survey to donors about past pregnancies	... (...)	gestational hypertension† 2/45 (4.4%) pregnancies preeclampsia* 2/45 (4.4%) pregnancies proteinuria* 2/45 (4.4%) pregnancies miscarriage* 6/45 (13.3%) pregnancies tubal *1/45 (2.2%) pregnancies 4/39 (10.2%) pregnancies required preterm hospitalization 39 viable births*
Reisaeter et al 2008 [b] (51)	106 pregnancies in 69 donors	Oslo, Norway (1967-2002)	A review of registry data	4.2 (...)	gestational hypertension‡ 3/106(2.8%) pregnancies preeclampsia‡ 6/106 (5.7%) pregnancies eclampsia* 0/106 (0%) pregnancies low birth weight[a] 9/106 (6.4%) pregnancies stillbirths[a] 3/106 (2.8%) pregnancies fetus born before 37 weeks gestation[a] 11/106 (10.8%) pregnancies fetal death less than 28 days after birth 0/106 (0%) pregnancies
Ibrahim et al 2009 [c] (49)	490 pregnancies in 239 donors	University of Minnesota, USA (1963-2007)	Mailed questionnaire	5.1 (...)	gestational hypertension 28/490 (5.7%) pregnancies preeclampsia 27/490 (5.5%) pregnancies gestational diabetes 13/490 (2.7%) pregnancies eclampsia among pregnancies was not reported full term birth 361/490 (73.7%) pregnancies prematurity 35/490 (7.1%) pregnancies fetal loss [d] 94/490 (19.2%) pregnancies

[a] In study by Buszta et. al one pregnancy was counted as two for the set of twins in their data. The woman who was pregnant and had not yet delivered was not counted in the outcome of miscarriage. [b] In study by Reisaeter a donor with chronic hypertension, defined by a blood pressure ≥140/90 mmHg prior to pregnancy or gestational week 20, was counted among the pregnancies after donation. [c] Study includes donors studied by Jones and Wrenshall et al. (...) Data not reported in the primary article. * Not defined. †Gestational hypertension defined as transient hypertension without proteinuria. ‡Gestational hypertension defined as new-onset blood pressure ≥140/90 mmHg after 20 weeks of gestation or an increase in diastolic blood pressure of at least 15 mmHg or systolic blood pressure of at least 30 mmHg from the woman's average blood pressure before 20 weeks of gestation, without proteinuria. With proteinuria in this setting it was defined as preeclampsia. Proteinuria was defined as excretion of ≥0.3 g per day, usually equivalent to ≥1+ on a standard urine test strip. [a]Low birth weight was ≤ 2500g. Birth weight was measured immediately after birth. A fetus was recorded as still born if it died before or during labour. Gestational age was based on last menstrual period. [d] Fetal loss includes fetal death, miscarriage and abortion.

The fifth study, published by Ibrahim et al. in 2009 reported a comparison between pregnancies before and after donation (49). They conducted a survey of female donors from a single centre years after their pregnancies. The response rate for the survey was 83%. They described 490 pregnancies in 239 donors after donation compared to 2,519 pregnancies among 846 women before donation. Compared to pregnancies before donation, pregnancies after donation had increased rates of gestational hypertension (0.6% vs. 5.7%, p-value=0.0001), preeclampsia (0.8% vs. 5.5%, p-value<0.0001), gestational diabetes (0.7% vs. 2.7%), prematurity (4.0% vs. 7.1%, p-value=0.0004) and fetal loss (11.3% vs. 19.2%, p-value<0.0001). Fetal loss included death, miscarriage and abortion. There were 361/490 (73.7%) full term births. Loss to follow up was 513/2102 (24%). 239 donors with pregnancies after donation had their renal function assessed about 20 years after donation (13 years after last pregnancy). The mean serum creatinine was 1.0 mg/dl (88μmol/L), 63/239 (26%) were hypertensive and 21/239 (9%) demonstrated proteinuria. As observed, there was a seven-fold increase in the risk of preeclampsia in post donation pregnancies. The authors reported that in absolute terms the incidence of adverse events observed in donors were similar to expected levels for the general population.

2.3. Present Studies

Available studies leave uncertainty about the true outcomes of pregnancy, as none have met the current epidemiological standards for accurate risk assessment (54). The literature itself was heterogeneous with respect to the ethnic populations sampled, risk factors considered, and methods of statistical analysis. Many of the cohort sizes were small, donors were frequently from single centre and studies were conducted retrospectively with incomplete follow-up. Events were ascertained by reviewing charts or asking patients to recall events years after pregnancy. Controls were often lacking with measurements made in a similar way to that of donors. When used, controls were not selected to be in as good health as kidney donors. These limitations make the data less reassuring than they should be.

Yet the results of the two newer studies by Reisaeter et al. and Ibrahim et al. extend current knowledge. Reisaeter et al. reported a complete sample of all pregnancies of 16

weeks or more for the entire country of Norway over three and a half decades. The number of pregnancies after donation is over two times the number reported by Wrenshall et al. The loss to follow-up was minimal, only through emigration. They provide an internal control group with similar measurements to those made in donors; although not completely characterized, the presence of undiagnosed chronic hypertension, kidney disease, or other co-morbidity in this control group of child-bearing women is certain to be low. Outcomes were defined. There was only a single pregnancy in a donor with chronic hypertension after donation. This reduces the concern that donation predisposes to chronic hypertension prior to pregnancy, which negatively impacts the pregnancy of donors. Reassuringly, there were also no cases of eclampsia reported after donation. Moreover, events were recorded at the time of pregnancy, reducing concerns about recall bias. Finally, definitive events like stillbirths and neonatal mortality were considered. Ibrahim et al. considered all the pregnancies for a single high volume transplant center in the United States over four decades. They reported no more than ten times the number of pregnancies after donation compared to Wrenshall et al. Provision of key predonation information (i.e. serum creatinine) and an analysis of long-term renal function after pregnancies are also major strengths of the paper.

In these recent studies there was an increase in both gestational hypertension and preeclampsia after donation compared to pregnancies before donation. The data suggest that a female donor's risk of developing a hypertensive disorder is increased by a few percent than if she had elected not to become a donor. However, women who become donors are selected for their excellent health, and the absolute risk of hypertensive complications after donation is still comparable to that observed in the general population (Table 1). In summary, it is of concern that, compared to the rate before donation, a higher rate of preeclampsia was observed after donation in the recent two studies.

CHAPTER 3- RATIONALE AND RESEARCH QUESTION

3.1. Uncertainty Remains

Current evidence still leaves questions and uncertainty for the health care professional wishing to disclose precise risks about maternal and fetal outcomes to a living donor. The primary question of interest is whether living kidney donors have a higher risk of adverse maternal outcomes compared to similar non-donor controls. All the previous studies did not provide measurements on group of controls similar in age, number of previous pregnancies, timing of those pregnancies, and previous history of pregnancy complications compared to donors who became pregnant after donation. Nor did they compare pregnancies after donation to pregnancies among controls adjusting for these factors. Mechanistically, matching the donors with controls on these factors may provide the best method of assessment of risk. Matching is done to reduce bias and increase precision in observational studies where randomization is not possible.

3.2. Creating New Knowledge in Maternal Health to Improve Health Care

In this study, the hypothesis that kidney donation significantly increases the risk of hypertensive disorders of pregnancy (gestational hypertension, preeclampsia, eclampsia) is examined. There were a number of reasons to perform this study; the results have important implications for the informed consent of female kidney donors and their follow-up to minimize complications should they become pregnant following nephrectomy.

Administrative data is defined as electronic information collected for financing or record keeping purposes by the administrator of a health service, typically a government or a health insurance provider (55-57). Health care in Canada is funded and delivered through publicly funded health care system. Canadians have universal access to health care, and Canadian researchers are in a good position to answer this question. In this study, existing administrative and provincial government payer datasets routinely collected for publicly funded health services are used. Anonymised health care records can be analyzed using encrypted identifiers to track individuals over time. Many of this type of data simply do not exist outside of Canada.

The databases used in this study are as follows: 1) Trillium Gift of Life Network (TGLN) was created in December 2000 by the Ontario Government and assumed the role of Ontario's central organ and tissue donation agency with the mission to significantly increase organ and tissue donation across the province and improve related processes and functions; 2) Ontario Diabetes Database (ODD) is a validated administrative data registry of Ontario residents for whom a diagnosis of diabetes is recorded in hospital discharge information or in claims for outpatient physician services (through the Ontario Health Insurance Plan); 3) The Canadian Institute for Health Information (CIHI) collects and analyzes information on health and health care in Canada and makes it publicly available. Canada's federal, provincial and territorial governments created CIHI as a not-for-profit, independent organization dedicated to forging a common approach to Canadian health information. CIHI's data and reports inform health policies, support the effective delivery of health services and raise awareness among Canadians of the factors that contribute to good health. CIHI DAD receives data directly from participating hospitals and is a national database for information on all separations from acute care institutions, including discharges, deaths, sign-outs and transfers. Following its inception in 1963, when it was developed to collect data on separations from institutions in Ontario, it has expanded to provide coverage in all provinces except Quebec; 4) A resident of Ontario is entitled to health care services paid for by the Ontario Health Insurance Plan (OHIP). The Ministry of Health and Long-Term Care pays for a wide range of services covered by OHIP; 5) The Registered Persons Database (RPDB) is used in various ministry-processing systems to verify eligibility for services. A significant use of the data is in the fee-for-service medical claims system where claims can be paid to the provider if the patient has eligibility and a valid health card.

These databases are linked at the Institute of Clinical Evaluative Sciences (ICES). ICES is an independent, non-profit research organization and is located in Sunnybrook Health Sciences Centre in Toronto and Queen's University in Kingston. Since its inception in 1992, ICES has played a key role in providing scientific insights to the research community. Health information at ICES is not examined on an individual basis and thus solely used for research and statistical purposes. All data are kept confidential to protect the privacy of the individuals.

Diagnoses and procedures are coded within administrative databases to facilitate record retrieval and synthesis of information. The most commonly used coding system worldwide is the International Classification of Diseases (ICD), which is published and maintained by the World Health Organization (WHO). There are two ICD platforms in use: the International Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10), and the International Classification of Disease, Ninth Revision, (ICD-9)(58). The Canadian Classification of Health Interventions (CCI), is a procedural coding scheme developed and maintained by the Canadian Institutes of Health Information Discharge Abstract Database (CIHI-DAD). Other codes frequently used in Ontario, Canada are the OHIP diagnoses and fee codes.

Living kidney donation and pregnancy outcomes are well coded within the Ontario health administrative databases, which makes this study feasible. Codes used to identify kidney donors and the hypertensive complications of pregnancy in female donors have good sensitivity and specificity as discussed in detail in the method section of this thesis. Codes used to detect secondary outcomes such as abruptio placentae, small for gestational age/intrauterine growth retardation, prematurity and low birth weight babies have also shown to have good sensitivity, specificity, and positive predictive value. It is recognized that even though the codes used in this study have good parameters, administrative databases are not primarily collected for research purposes and therefore may not be as accurate as original data collection. However, administrative data reflects the actual care given to patients; it allows researchers to assess the effectiveness of an intervention at a population level.

3.3. This Study could have Many Immediate Benefits

A study quantifying the risk of kidney donation on pregnancies of living kidney donors is both timely and important. The number of living kidney donor transplants grew over the last decade, with 62% of countries reporting at least a 50% increase (9). There is an accelerated growth in living kidney donation without proper evidence of the maternal and fetal risks involved. This study would also have many immediate benefits. It will provide physicians with a precise estimate of risk involved in this population. It will also aid in the design of future prospective studies. The study results could help in the informed con-

sent of female donors and make clear decisions on their act of altruism. Finally, it will help the broader audience of health administrators and policy makers to advocate guidelines regarding donation and health care during pregnancy of living kidney donors.

3.4. Objectives

3.4.1. Primary Research Question

Do living kidney donors, have an increased risk of hypertensive complications of pregnancy (gestational hypertension, preeclampsia, and eclampsia) compared to non-donor controls?

3.4.2. Hypothesis

Female living kidney donors will be at significantly increased risk of gestational hypertension, preeclampsia, and eclampsia during the first post-donation pregnancy as compared to healthy non-donors.

3.4.3. Secondary Research Question

Do living kidney donors have an increased risk of worse maternal and fetal outcomes compared to healthy non-donor controls? Maternal and fetal outcomes include the individual components of the primary outcome such as gestational hypertension, preeclampsia, and eclampsia. Other secondary outcomes include abruptio placentae, small for gestational age / intrauterine growth retardation, and prematurity / low birth weight babies.

CHAPTER 4- METHODS

4.1. Study Overview and Setting

This is a retrospective matched cohort study using linked Ontario administrative databases. The study is reported according to recommended Strengthening the Reporting of Observational Studies in Epidemiology Statement (STROBE) guidelines (59). The STROBE checklist includes items on the statement of hypotheses, eligibility criteria, study population, power and sample size calculations, definition of outcomes, loss to follow-up, and missing data. Pregnancy outcomes among donors to non-donor controls were compared by linking Trillium Gift of Life Network (TGLN) to health administrative data stored at the Institute for Clinical Evaluative Sciences (ICES) in Toronto. All administrative database codes used were validated against manual chart review / chart reabstraction. The same method of outcome ascertainment was used for both donors and controls. Donors and controls were matched on important variables. Ten non-donor controls for every donor were selected. Follow-up through universal health records is almost perfect since emigration from the province of Ontario is less than 1% per year. Women can have more than one pregnancy after donation, which are not statistically 'independent' events. The primary analysis focused on the first pregnancy after donation to help the results be easily interpreted and believed by clinicians.

4.2. Data Sources and Data Collection

Citizens of Ontario have universal access to hospital care and physician services through the Ontario Health Insurance Plan (OHIP). Anonymised health care records were analysed using encrypted OHIP identifiers to track individual health care utilization over time. These databases are held at the Institute for Clinical Evaluative Science (ICES) in Toronto. The five databases as shown in Table 3 are as follows:

(1) the Trillium Gift of Life Network (TGLN) Database, which records information for donors and recipients in Ontario undergoing kidney transplantation. Data from the TGLN spanned the time from December 1991 to December 2005.

(2) the Ontario Diabetes Database (ODD), which is a registry of Ontario residents diagnosed with diabetes was considered from the period July 1991 to March 2007.

(3) the Canadian Institute for Health Information (CIHI) - Discharge Abstract Database (DAD), records hospital admissions including diagnostic and procedural information. Data was considered from July 1991 to March 2007. As pointed out earlier, the Canadian Institute for Health Information Discharge Abstract Database (CIHI DAD) used the International Classification of Disease Ninth Revision (ICD-9) coding until the year 2002, at which point there was a switch to ICD-10 coding. To span our timeframe, both ICD-9 and ICD-10 codes were used to delineate baseline characteristics and outcomes.

(4) the Ontario Health Insurance Plan (OHIP) Database, which provides information on physician and allied health claims for inpatient and outpatient services was considered from July 1991 to March 2007; and

(5) the Registered Persons Database (RPDB), which contains vital statistics on Ontario residents. The RPDB database gives the demographic information on all persons who have ever received an Ontario health card number.

The latter four databases have been used extensively in population-based health outcome research (60-62).

Table 3: Databases used and periods of available data

Database	Period	Description of Data
TGLN Living Donor Data	Dec 1991 - Dec 2005	Data from Trillium Gift of Life Network
ODD	Jul 1991 - Mar 2007	Ontario diabetes incidence and prevalence data
CIHI	Jul 1991 - Mar 2007	Inpatient hospitalization data
OHIP	Jul 1991- Mar 2007	Claims paid by OHIP
RPDB	Jul 1991 - Mar 2007	Demographic information on all persons who have ever received an Ontario health card number

4.3. Time Frame

4.3.1. Cohort entry

Datasets from July 1st 1991 to March 31st 2007 or until the time of availability were reviewed. As shown in figure 2, the date of delivery was used as the cohort entry date. At the time of patient identification certain baseline characteristics such as age, residency (rural versus urban), socio-economic status, the year and quarter of date of delivery, any previous history of hypertensive complications during pregnancy, number of previous pregnancies (since 1991) and year and quarter of last pregnancy were identified. Other variables of interest included donor race, donor relationship to recipient, age at time of donation, year and quarter of donation and years since donation.

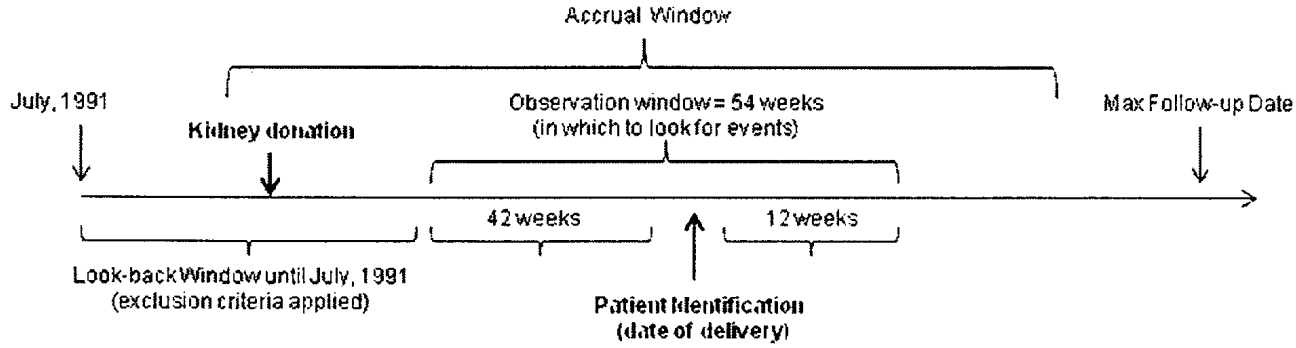
4.3.2. Accrual window

The date of accrual started from July 1993 to December 2006, during which women who had their first childbirth after donation were identified.

4.3.3. Observation period

As the primary event could occur any time after 20 weeks of gestation until 12 weeks after delivery, the observation window extended 42 weeks before the date of childbirth until 12 weeks after. This was the period when the primary and secondary outcomes were observed.

Figure 2: Time frame definitions



Accrual Start / End Dates	July 1993 to December 31, 2006
Max Follow-up Date	March 31, 2007
When does observation window terminate for the analysis of any given outcome?	The first of the following dates (in order): • Date of event (date of occurrence of outcomes of interest) • 12 weeks after patient date of delivery (date of identification/cohort entry) • March 31, 2007
Period of Outcome Assessment	Look 42 weeks before to 12 weeks after patient identification
Look-back Window	July, 1991

4.3.4. Look-back window

Each patient identified had a variable look back window with a minimum of 2 years from the date of cohort entry (patient identification) until July 1991. Women were excluded from the study if they met one of our exclusion criteria such as women who had kidney failure and receiving dialysis, women who were diabetic and women who were hypertensive. Non-donor control women were excluded if they had kidney disease either congenital or acquired, as these individuals would never be considered healthy enough to become a donor. Donors and non-donor controls were made as comparable to one another

at the time of selection. Furthermore, they were matched on important variables: age at the time of delivery, socio-economic status, time of previous delivery, history of previous pregnancy with hypertensive complications, and multiple gestation in the current pregnancy. They were also matched on the year and quarter of cohort entry to account for any secular trends in child bearing and birth.

4.4. Measures of validity

Codes were validated by reporting the sensitivity, specificity, positive predictive value (PPV) and agreement with chart review or chart reabstraction as reference standards.

Sensitivity = TP / (TP + FN)

Sensitivity is a measure of the proportion of true positives that are correctly coded as having a specified condition or procedure according to the reference standard.

Specificity = TN / (FP + TN)

Specificity is a measure of the proportion of true negatives that are correctly coded as not having a specific condition or procedure according to the reference standard.

Positive Predictive Value (PPV) = TP / (TP + FP)

PPV is the proportion of those who truly have the condition among those coded to make the condition or procedure.

Agreement is probably the most simple and least robust measure. It is the number of times a code is assigned by each rater and then divides this number by the total number of codes referring it to the reference standard (chart review / chart reabstraction). It does not take into account that agreement may happen solely based on chance.

4.5. Participant Eligibility

Individuals were considered eligible to be included in the study when they met the following criteria:

(1) Exposed individuals (donors): Female living kidney donors were identified by multiple data sources who were at least 20 weeks pregnant. Since identifying individuals with 20 weeks pregnancy can be challenging in a dataset, we proposed to identify any individual who delivered a fetus either live or stillborn. Stillborn is defined as birth of a dead fetus after 20 weeks of pregnancy.

(2) Unexposed (controls): Women from the general population who were at least 20 weeks pregnant and have never donated a kidney.

It was necessary to identify women who carried their pregnancy to at least 20 weeks gestation as our primary outcome of hypertensive disorder of pregnancy cannot develop until after 20 weeks gestation.

4.5.1. Donors

Female kidney donors who were less than 49 years of age at the time of donation (childbearing age) using Trillium Gift of Life data were identified. Women who came from outside the province to donate a kidney to a recipient in Ontario were not considered. Traditionally, transplant programs did not accept anyone with a history of hypertension as a living kidney donor. However, to meet the demands for kidneys, in recent years some programs have accepted a small number of individuals with hypertension well controlled on a single medication (63). In this study, any woman with a history of hypertension prior to kidney donation was excluded, as the numbers anticipated were too few to allow for meaningful assessment. Any women who developed kidney failure, diabetes mellitus or hypertension after donation but prior to becoming pregnant was also excluded. These numbers were expected to be very small, and the mechanisms by which these women develop complications during pregnancy differ from the routine donor seen in clinical care.

Pregnancy: Donors who became pregnant after donation were identified. Only the first pregnancy after donation in women who had multiple pregnancies was considered. All women who carried a pregnancy to at least 20 weeks gestation were identified, as the primary outcome of hypertensive disorders of pregnancy cannot be ascertained until after 20 weeks. When a woman had a code for any of the following conditions, it indicated that a pregnancy did occur: normal vaginal delivery, caesarean section delivery, breech delivery, malpresentation at delivery, operational delivery other than caesarean section (forceps delivery, vacuum extraction), pre-term delivery (live births before 37 weeks of gestation) (64), post-term delivery, single birth (live or stillborn), multiple births (live or stillborn). The codes used to identify the events are presented in Table 4. Many of the codes were found to be valid. Validation was performed against a reference standards of

chart review (65-67) or chart abstraction (68). The date of the first of these events was considered the date of patient identification. Diagnostic conditions were considered present in the discharge abstract for any hospitalization if it was listed as the primary diagnosis or any diagnosis. Approximately 95% of Ontario physicians operate under the fee for service payment structure of the Ontario Health Insurance Plan. It was expected that the sensitivity and positive predictive value of procedure codes was high (69). Evidence from other fee for service payment systems in Alberta, Canada show high estimates of sensitivity with major surgical procedures (70). The period before and after identification (42 weeks before to 12 weeks after) was used to ascertain events / complications of pregnancy.

Table 4: Codes used to ascertain women who delivered a fetus

CONDITION	DATABASE	CODES	VALIDITY[†]
Normal vaginal delivery	CIHI – diagnostic	**ICD-9** 650	
	CIHI – procedural	**CCP** 87.98	
	CIHI – diagnostic	**ICD-10** O80, O75701, O75703, O75709	
	CIHI – procedural	**CCI** 5MD50	Sensitivity: 98% (68) Specificity: 100% (68) Positive predictive value: 97% (68)
	OHIP – diagnostic[‡]	**OHIP Dxcode** 650	
	OHIP – procedural[‡]	**OHIP fee code** P006	
Caesarean section delivery	CIHI – diagnostic	**ICD-9** 6697	
	CIHI – procedural	**CCP** 86.0	
	CIHI – diagnostic	**ICD-10** O82	
	CIHI – procedural	**CCI** 5MD60	Sensitivity: 99% (68) Specificity: 100% (68) Positive predictive value: 100% (68)
	OHIP – procedural[‡]	**OHIP fee code** P018, P041, P042	
Breech delivery	CIHI – diagnostic	**ICD-9** 6696	Sensitivity: 89.4% (65) Specificity: 99.7% (65) Positive predictive value: 97.9% (65)
	CIHI – procedural	**CCP** 84.5, 84.51, 84.52, 84.53, 84.6, 84.61, 84.62, 84.69	
	CIHI – diagnostic	**ICD-10** O32101	
	CIHI – procedural	**CCI** 5MD56	
Malpresentation at delivery	CIHI – diagnostic	**ICD-10** O32201, O32301, O32401, O32501, O32601, O32801, O32901	
Operational delivery other than caesarean section	CIHI – diagnostic	**ICD-9** 6695	Sensitivity: 85-90% (67) Specificity: 99.2% (67) Positive predictive value: 85-93% (67)
	CIHI – procedural	**CCP** 84.0, 84.1, 84.2, 84.21, 84.29, 84.3, 84.31, 84.39, 84.4, 84.7, 84.71, 84.79, 84.8, 84.9	
	CIHI – diagnostic	**ICD-10** O81	
	CIHI – procedural	**CCI** 5MD53, 5MD54, 5MD55	Sensitivity: 97% (68) Specificity: 100% (68) Positive predictive value: 97% (68)
	OHIP – procedural[‡]	**OHIP fee code** P020	
Pre-term delivery	CIHI – diagnostic	**ICD-9** 6442	Sensitivity: 75-84.4% (66;67) Specificity: 99.2-99.5% (66;67) Positive predictive value: 92.7-95% (66;67)
	CIHI – diagnostic	**ICD-10** O60, O75801, O75802, O75803, O75804, O75809	Agreement: 92.3% (68)
Post-term delivery	CIHI – diagnostic	**ICD-10** O48	Agreement: 83.8% (68)
Single birth (live)	CIHI – diagnostic	**ICD-9** V270	
		ICD-10 Z370	
Single birth (stillborn)	CIHI – diagnostic	**ICD-9** V271	
		ICD-10 Z371	
Multiple births	CIHI – diagnostic	**ICD-9** V272-V277	Sensitivity: 95-100% (66;67) Specificity: 100% (66;67) Positive predictive value: 100% (66;67)
	CIHI – diagnostic	**ICD-10** O84, O30001, O30101, O30201, O30801, O30901, Z372-Z375, Z376-Z377, Z379	

Abbreviations: **CCI**, Canadian Classification of Health Interventions; **CCP**, Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures; **CIHI**, Canadian Institute for Health Information discharge abstract database; **ICD-9-CM**, International Classification of Disease, Ninth Revision, Clinical Modification; **ICD-10**, International Classification of Disease, Tenth Revision; **OHIP**, Ontario Health Insurance Plan database. [†]Validation performed against the following reference standards: chart review (65-67)and chart abstraction (68). Diagnostic conditions were considered present in the discharge abstract for any hospital if it was listed as the primary diagnosis (68) or any diagnosis (65-67). [‡] Approximately 95% of Ontario physicians operate under the fee for service payment structure of the Ontario Health Insurance Plan. It was expected that the sensitivity and positive predictive value of these procedure codes was high (69). Evidence from other fee for service payment systems in Alberta, Canada show high estimates of sensitivity with major surgical procedures (70).

4.5.2. Controls

Non-donors (controls) were randomly selected from healthy women residing in Ontario. Controls were matched to donors on the following important risk factors for hypertensive disorders of pregnancy ascertained using administrative data:

(1) age within one year at the time of pregnancy (older age is associated with greater risk (71));

(2) year and quarter of cohort entry date (to account for any secular trends (72));

(3) history of previous pregnancy with hypertensive complications (previous uneventful pregnancies reduce the risk (73));

(4) year and quarter of last previous delivery (a greater interval from a previous pregnancy increases the risk (74));

(5) multiple gestation in the current pregnancy (multiple gestations increase the risk (73)); and

(6) socioeconomic status based on neighbourhood income quintile (lower socioeconomic status increases the risk (75)).

Pregnancies were identified in the same manner in controls as donors. In this study an individual could only be selected as a control for a maximum of one donor. Kidney donors go through a rigorous selection process to confirm they are in excellent health prior to kidney donation. To select non-donor controls who are also in excellent health, any individual who had evidence of kidney disease or systemic lupus erythematosus prior to the time their matched donor had their nephrectomy were excluded. The codes used for exclusion and matching, and their validation, are presented in Table 5.

Table 5: Codes used in exclusion and matching

CONDITION	DATABASE	CODES	VALIDITY†
Multiple births	CIHI – diagnostic	**ICD-9** V272-V277	Sensitivity: 95-100% (66;67) Specificity:100% (66;67) Positive predictive value: 100% (66;67)
	CIHI – diagnostic	**ICD-10** O84, O30001, O30101, O30201, O30801, O30901, Z372-Z375, Z376-Z377, Z379	
Kidney Failure	CIHI – diagnostic	**CCP** 5195, 6698	
		CCI IPZ 21	
	OHIP – diagnostic OHIP - procedural	Fee codes: R849, G082, G083, G085, G090, G091, G092, G094, G095, G096, G294, G295, G323, G325, G326, G330, G331, G332, G333, G860, G861, G862, G863, G864, G865,G866	
Diabetes Mellitus	ODD	*ODD codes	
Hypertension	CIHI [a]	**ICD-9 CM** 410x-405x	Sensitivity:84% (76) Specificity: 88% (76) Positive predictive value: 77% (76)
		ICD-10 I10-I13,I15	
	OHIP [n]	401,402,403	Sensitivity: 73-84% (76) Specificity: 88-95% (76) Positive predictive value: 77-87% (76)
Systemic lupus erythematosus	OHIP- diagnostic	710	

Abbreviations: **CCI**, Canadian Classification of Health Interventions; **CCP**, Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures; **CIHI**, Canadian Institute for Health Information discharge abstract database; **ICD-9-CM**, International Classification of Disease, Ninth Revision, Clinical Modification; **ICD-10**, International Classification of Disease, Tenth Revision; **OHIP**, Ontario Health Insurance Plan database.
†Validation performed against the following reference standards: chart review (66;67)and chart abstraction and recoding (76). Diagnostic conditions were considered present in the discharge abstract for any hospital if it was listed as the primary diagnosis or any diagnosis (66;67).
*Ontario Diabetes Database (ODD) uses validated codes derived from other administrative databases (77).
[a] Algorithm used: Diagnosis present in the discharge abstract of any hospitalization OR at least two physician outpatient claims, [n] diagnosis present in at least two physician outpatient claim/claims.

4.6. Exclusion Criteria

Both donors and controls were excluded if they had any of the below mentioned conditions. Exclusion criteria were applied for individuals during the look-back window period. Individuals were excluded if there was evidence of any of the following more than 42 weeks prior to the time a participant was identified as delivering a fetus. A 42-week period was chosen since pregnancy is not allowed to continue past 42 weeks and the ex-

clusion criteria were meant to be applied to the time just prior to the start of pregnancy. Normally labour is induced between the 40 and 42 weeks gestation.

4.6.1. Exclusion Criteria (for donors and controls)

1. Kidney failure receiving dialysis

   Kidney failure is defined as a situation in which the kidneys fail to function adequately. It can be either acute or chronic and is typically detected by elevated serum creatinine or decrease in glomerular filtration rate (GFR). Dialysis is primarily used to provide an artificial replacement for those with kidney failure. The different codes used to identify such individuals are as below. Such individuals were excluded to ensure that no kidney recipients were accidentally coded as donors.

   CCP: 5195 [Hemodialysis], 6698 [Peritoneal dialysis]; CCI: 1PZ21 [Dialysis, urinary system]; OHIP fee code: R849 [Dialysis initial and acute], G082, G083, G085, G090, G091, G092, G094, G095, G096 [Continuous HD] , G294, G295 [Ultra filtration], G323, G325, G326 [Hemodialysis] , G330, G331, G332 [Peritoneal dialysis], G333 [Home/self care dialysis], G860 [Hemodialysis – hospital location], G861 [Peritoneal dialysis – hospital location], G862 [Hospital self care dialysis], G863, G864, G865, G866 [Dialysis unspecified]

2. Diabetes mellitus

   Diabetes mellitus is defined as a condition that is characterized by high blood glucose and relative insulin deficiency. Diabetes mellitus via the Ontario Diabetes Database (ODD) uses validated codes derived from other administrative databases. Women with such a condition have an increased risk of developing hypertensive disorders of pregnancy.

3. Hypertension

   Hypertension also referred to as high blood pressure, is a medical condition in which there is an elevation of systolic blood pressure > 140mmHg and a diastolic blood pressure of > 90 mmHg. Women were excluded if they had a code for hypertension in CIHI ICD-9: 401x-405x in any of the 16 diagnostic fields; ICD-10: I10-I13, I15 in any of the 16 diagnostic fields; presence of at least two OHIP

DxCodes for hypertension in OHIP. OHIP DxCodes: 401, 402, 403. This was done to ensure that women were not at an increased risk of developing the primary outcome of interest prior to cohort entry.

4.6.2. Exclusion criteria (for controls only)

1. Kidney disease / Glomerulonephritis

Kidney disease includes a wide range of disorders. However, the most common causes of kidney disease include diabetes, high blood pressure, and "hardening of the arteries" (which damages the blood vessels in the kidney). Some kidney diseases are caused by an inflammation of the kidneys, called nephritis. This may be due to an infection or to an autoimmune reaction where the body's immune or defence system attacks and damages the kidneys. Other kidney diseases, such as polycystic kidney disease are caused by problems with the shape or size of the kidneys (anatomic disorders). Those with such kidney diseases with the following codes were excluded from the study.

ICD-9: 581 [Nephrotic syndrome], 582 [Chronic proliferative nephritis], 583 [Nephritis], 584 [Acute renal failure], 585 [Chronic renal failure], 586 [Renal Failure], 587 [Renal Sclerosis NOS], 588 [Impaired renal function], 7885 [Oliguria and anuria], 753 [Renal Agenesis], 403 [Malignant hypertension with renal disease], 405 [Malignant reno-vascular hypertension], 593 [Nephroptosis]; ICD-10: N17 [Acute renal failure], N18 [Chronic renal failure], N19 [Renal failure, unspecified], N01 [Rapidly progressive nephritic syndrome], N03 [Chronic nephritis], N25 [Diffuse mesangio capillary necrosis], NO52 [Unspecified nephritic syndrome], N053-55 [Unspecified nephritic syndrome], NO72-74 [Hereditary nephropathy; Glomerulonephritis], I12 [Hypertensive renal disease], I13 [Hypertensive heart and renal disease], R34 [Oliguria and Anuria]; OHIP DxCodes: 580 [Acute Glomerulonephritis], 581 [Nephrotic syndrome], 584 [Acute renal failure], 585 [Chronic renal failure, uremia]

2. Systemic Lupus Erythematosus:

   Systemic Lupus erythematosus is defined as an autoimmune disease that can cause inflammation of various internal organs of the body as well as the skin. Those identified to have lupus were excluded from the study as such individuals would never be considered healthy enough to become a donor. Codes used to identify such individuals are as follows: OHIP DxCodes: 710

4.7. Primary Outcome: Hypertensive Disorders of Pregnancy

The primary outcome of interest was hypertensive disorders of pregnancy, which is a composite outcome of gestational hypertension, preeclampsia or eclampsia. About 10% of pregnancies in the general population are thought to be affected by new hypertensive disorders of pregnancy (78;79).

4.7.1. Definitions:

As discussed in Table 6 the definitions of the individual component of the composite outcome of hypertensive disorders of pregnancy is as below:

Gestational Hypertension: Gestational hypertension, formerly known as pregnancy-induced hypertension or PIH, is defined as new onset hypertension after 20 weeks gestation ($\geq$ 140 mm Hg systolic *or* $\geq$ 90 mm Hg diastolic of two elevated blood pressure measurements 6 hours apart).

Preeclampsia: Preeclampsia is defined as gestational hypertension plus proteinuria (defined as > 0.3 g / 24 hours or two readings of 1+ proteinuria on dipstick at least 6 hours apart).

Eclampsia: Eclampsia is defined as new onset of general tonic-clonic convulsions in a woman with preeclampsia.

Table 6: Composite outcome assessment of hypertensive disorders of pregnancy*

Clinical Findings (>20 weeks pregnant)	Gestational Hypertension	Preeclampsia	Eclampsia
Hypertension[1]	+	+	+
Proteinuria[2]	–	+	+
Seizures[3]	–	–	+

*Hypertensive disorders of pregnancy consists of gestational hypertension, preeclampsia and eclampsia

[1] Hypertension is defined as two elevated blood pressure measurements, >140 systolic or >90 diastolic, 6 hours apart
[2] Proteinuria is defined as two readings of 1+ proteinuria on dipstick 6 hours apart or ≥ 300 mg of protein in 24 hour urine in the absence of a urinary infection
[3] Seizures is defined as the new onset of general tonic-clonic convulsions in a woman with preeclampsia

4.8. Importance of Primary Outcome

The importance of well-controlled blood pressure during pregnancy is undeniable. Clinical practice guidelines recommend blood pressure be judiciously measured and followed during pregnancy (78). Hypertensive disorders of pregnancy are leading causes of maternal, fetal and neonatal morbidity and mortality worldwide (80-82). They are among the five most common causes of maternal deaths (81). Developing preeclampsia may have a lasting impact on the risk of subsequent renal and cardiovascular disease (83;84); the concern is even greater in a kidney donor with a single remaining kidney.

4.9. Coding of Outcome

The outcome of hypertensive disorders of pregnancy was preferentially defined using codes that have previously been shown to have good validity when health administrative data is compared to chart review and chart reabstraction / recoding. These codes are presented in Table 7 and 8 below.

Table 7: Validity of codes used in primary outcome

CONDITION	DATABASE	CODES	VALIDITY[†]
Gestational hypertension	CIHI - diagnostic	**ICD-9** 6429	
	CIHI - diagnostic	**ICD-10** O13001-O13004, O13009	Sensitivity: 68.2%(85) Specificity: 99.6%(85) Positive predictive value: 94.4%(85)
Preeclampsia	CIHI – diagnostic	**ICD-9** 6424, 6425	Sensitivity: 69.7-100% (66;67) Specificity: 98.9-100% (66;67) Positive predictive value: 77-100% (66;67)
	CIHI – diagnostic	**ICD-10** O14001-O14004, O14009	
Eclampsia	CIHI – diagnostic	**ICD-9** 6426	Sensitivity: 50-100% (66;86) Specificity: 99.9-100% (66;86) Positive predictive value: 100% (66;86)
	CIHI – diagnostic	**ICD-10** O15001, O15003, O15101, O15103, O15201, O15203, O15209	
	OHIP – diagnostic	**OHIP** DxCode 642	

Abbreviations: CIHI, Canadian Institute for Health Information discharge abstract database; **ICD-9**, International Classification of Disease, Ninth Revision; **ICD-10**, International Classification of Disease, Tenth Revision; **OHIP**, Ontario Health Insurance Plan database.

[†]Validation performed against chart review as reference standard (66;67;85;86). Diagnostic conditions were considered present in the discharge abstract for any hospitalization if it was listed as the primary diagnosis or any diagnosis (66;67;85;86).

4.10. Secondary Outcomes

Clinically important secondary outcomes included the individual components of the primary outcome as well as the conditions described below. The codes used and their validity are given in Table 8. These outcomes were selected for their clinical importance. It is recognized that for some secondary outcomes, the sample size was small and underpowered for modest effects. The analyses of these secondary outcomes were considered exploratory.

Table 8: Codes used to ascertain secondary outcomes

CONDITION	DATABASE	CODES	VALIDITY[*†]
Abruptio placentae	CIHI – diagnostic	**ICD-9** 6412	Sensitivity: 89%(67) Positive predictive value:89%(67)
		ICD-10 O45	
Small for gestational age (SGA), intrauterine growth restriction (IUGR)	CIHI – diagnostic	**ICD-9** 7649, 7640, 7641	
	CIHI – diagnostic	**ICD-10** P0590, P0591, P0599,	Agreement: 50%(68)
Prematurity, low birth weight (LBW)	CIHI – diagnostic	**ICD-9** 7650	
	CIHI – diagnostic	**ICD-10** P070, P071, P072, P073	Sensitivity: 93%(68) Specificity: 100%(68) Positive predictive value: 89%(68)
	OHIP – diagnostic[‡]	**OHIP** Dxcode 765	

Abbreviations: **CCI**, Canadian Classification of Health Interventions; **CCP**, Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures; **CIHI**, Canadian Institute for Health Information discharge abstract database; **ICD-9**, International Classification of Disease, Ninth Revision, Clinical Modification; **ICD-10**, International Classification of Disease, Tenth Revision; **OHIP**, Ontario Health Insurance Plan database;

[*] Validation was performed in Canada (68)

[†] Validation performed against the following reference standards: chart review(67) and chart abstraction / recoding(68). Diagnostic conditions were considered present in the discharge abstract for any hospital if it was listed as the primary diagnosis (68) or any diagnosis (67).

[‡] Approximately 95% of Ontario physicians operate under the fee for service payment structure of the Ontario Health Insurance Plan. It was expected that the sensitivity and positive predictive value of these procedure codes was high (69). Evidence from other fee for service payment systems in Alberta, Canada show high estimates of sensitivity with major surgical procedures (70).

4.10.1. Abruptio placentae

An abruptio placenta (also known as placental abruption) is a complication of pregnancy wherein the placental lining has separated from the uterus of the mother. There is an increased risk of placental abruption in women with hypertensive complications compared to those with normal blood pressure during pregnancy (87). It is the most common cause of late pregnancy bleeding. Abruption refers to the abnormal separation of the placenta and can occur from 20 weeks of gestation to just prior to birth. It occurs in 1% of pregnancies worldwide with a fetal mortality rate of 20-60% and maternal mortality rate of 0.5 to 5% depending on the degree of separation (88-90).

4.10.2. Small for Gestational Age (SGA) / Intrauterine Growth Retardation (IUGR)

Vascular supply to the placental bed can be compromised in pregnancies with hypertensive disorders (91). According to one study, intrauterine growth retardation was observed more frequently in women with hypertensive disorders (12%) than in healthy controls (5%) (87). The most widely used definition of SGA / IUGR is a fetus whose estimated weight is below the 10th percentile for its gestational age. At term, the cut off birth weight for IUGR is 2,500 g (5 lb, 8 oz) (92).

Table 9: Studies from the general population on the incidence of premature birth and low birth weight

Study [n], year	Primary location	Population (N)	Years of recruitment	Premature birth (%) ¥	Low birth weight (%) ‡
Tallo CP 1995† (93)	Rhode Island, USA	62	1988-1993	2.0	3.0
Nuojua-Huttunen S 1999 ₸ (94)	Oulu, Finland	276	1991-1996	5.1	6.2
Koudstaal J 2000 □ (95)	Amsterdam, Netherlands	307*	(...) - 1992	5.9	6.9
Isaksson R 2002† (96)	Helsinki, Finland	345*	1993-1999	10.1	5.8
Dhont M 1997 ₸ (97)	Ghent, Belgium	622*	1990-1995	10.5	11.2
Lundsberg LS 1997 [a] (98)	New Haven, USA	2 714	1988-1992	3.0	3.8
Addor V 1998 [a] (99)	Vaud, Switzerland	6 088*	1993-1994	4.6	4.8
Berardi A 2009 [a] (100)	Emilia-Romagna, Italy	112 933	2003-2005	7.4	(...)
Martin J 2009 Ψ (101)	Maryland, USA	4 265 996	2006	12.8	8.3

[n] Studies are arranged by sample size. Results reported are for singleton pregnancies.
(...) Eclipses denote data not reported in the study.
¥ Premature birth was defined as less than 37 weeks of completed gestational age at the time of delivery.
‡ Low birth weight was defined as <2500g at the time of delivery.
† Studies were single centre, retrospective; ₸ case control.
[a] Studies are multicentre, prospective; □ case control; Ψ national vital statistics.
*Outcomes were based on the number of pregnancies; other studies were based on number of live births.

4.10.3. Prematurity / low birth weight

Premature birth is defined as birth before 37 weeks of gestation. The frequency of premature birth in the United States increased from 10.7% in 1992 to 12.3% in 2003 (102). Women with hypertensive disorders of pregnancy delivered prematurely more often than healthy controls (30% vs.14%) (87). This can be partly due to induction of labour (103).

Premature birth and low birth weight have an overall incidence of 2 to 13% in the general population (Table 9).

4.11. Other outcomes

4.11.1. Surveillance outcome

There is a theoretical concern that after transplantation donors may have more detailed follow-up during pregnancy by their physicians compared to non-donor controls. Irrespective of physiology, this could result in a higher proportion of living donors being diagnosed with hypertensive disorder of pregnancy compared to non-donors. Overall, it is believed that this possible 'information bias' was unlikely given the standard of care for all pregnant women to have their blood pressure measured regularly throughout pregnancy. To prove this, donors and controls were compared on the average number of health care visits each woman has during their pregnancy. Visits for pregnancy care to either a family practitioner or obstetrician as an antenatal / prenatal visit during the pregnancy were counted.

Table 10: Codes used to ascertain surveillance outcomes

CONDITION	DATABASE	CODES
Prenatal / antenatal visits	CIHI – diagnostic	**ICD-9** V220, V221, V230, V231, V232, V233, V234, V235, V238, V239, V288, V289
		CCP 02.88
		ICD-10 Z34, Z35
		CCI 5AB01, 5AB03
	OHIP - diagnostic	**OHIP** DxCode 970
	OHIP - procedural	**OHIP** fee code P003, P004, P005

CCI, Canadian Classification of Health Interventions; **CCP**, Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures; **CIHI**, Canadian Institute for Health Information discharge abstract database; **ICD-9**, International Classification of Disease, Ninth Revision, Clinical Modification; **ICD-10**, International Classification of Disease, Tenth Revision; **OHIP**, Ontario Health Insurance Plan database

4.12. Statistical Analysis

Matching is used in retrospective comparative studies to increase the validity of inferences by controlling for confounding, rather than for increasing precision / efficiency (104). The loss of efficiency in retrospective studies relates to the fact that matching fac-

tors are correlated with exposure. Otherwise, efficiency is not affected by matching (105). It is known that if the effect of a factor is in doubt, the preferable strategy is not to match but control for it in the statistical analysis (104).

Baseline characteristics used for matching donors and non-donor controls were not tested for statistical significance. For baseline characteristics that were not matched, Mantel Haenszel chi-square test was used to test for significance. The fact that the test is a summation of random variables and thus tends to approach normality rapidly, makes this test valid for a matched sample situation (106).

The generalized estimating equations (GEE) method is being increasingly used to analyze longitudinal and other correlated data, especially when they are binary or in the form of counts (107). In this thesis generalised estimating equations (GEEs) were used to estimate the association between donation and outcomes (primary, secondary) (108). The potential advantages of the GEE approach for estimating models with correlated data are several. First, it primarily accounts for the form of within-subject correlation. At the same time, the estimates obtained through application of these models are robust to misspecification of correlations. This is an important trait, since understanding of those relationships is often imperfect at best. Additionally, the model also provides an opportunity to gain substantive insight to assess the effect of covariates on the conditional correlation among observations (108). This analysis provided the odds ratio (OR) of developing a hypertensive disorder of pregnancy in kidney donors compared to controls. No additional variables were considered in the primary models; matching variables were accounted for by the study design and the correlation of matches were accounted for in the model. All analyses employed a two-tailed alpha level of 0.05 to determine statistical significance. All analyses were performed using SAS version 9.13 (SAS Institute Inc., Cary NC).

4.12.1. Statistical power

To perform the sample size calculations a precise estimate of the expected incidence of the primary outcome (hypertensive disorders of pregnancy) among our controls needed to be derived. To do so, nine well conducted prospective studies which characterized the incidence of hypertensive disorder of pregnancy were reviewed (Table 1). An incidence rate of 10% was estimated from these studies. As the study is a matched retrospective cohort design, the correlation between exposure (donation) and matching variables needed to be accounted for, which reduced the efficiency of the test, but increased validity by controlling for confounding (105). In other words, if there was no association between donor and matched control (i.e. matching was ineffective), the probability of discordance is easily calculated using the detectable OR and the baseline risk of disease. However if the matching is effective (i.e. variables used to match are associated with exposure), then variation of exposure probabilities across matches should be estimated (i.e. how successful the matching has been), and incorporated in the sample size calculations. The stronger the association between matching factors and exposure status, the greater the sample size requirements.

As seen in Table 11, at least 187 donors and 1870 controls, were needed to detect an odds ratio of 2.0 or more to detect the risk of the primary outcome among donors when compared to non-donor controls. Calculations were done to have a statistical power of 0.8, with two sided type 1 error of 0.05, with the donor to non-donor controls ratio of 1:10. A continuity correction of Ψ=1.25 (where Ψ is a measure of the association between donors and their matched controls) was incorporated.

Table 11: Sample size calculations, number of donors

	Event rate in controls									
Odds ratio to detect	**5%**	**6%**	**7%**	**8%**	**9%**	**10%**	**11%**	**12%**	**13%**	**14%**
1.75	529	449	393	351	318	292	271	253	238	225
2.00	335	286	250	224	203	187	174	163	153	146
2.25	239	204	179	161	146	135	125	118	111	106
2.50	183	156	138	124	113	104	97	91	86	82
2.75	147	126	111	100	91	84	79	74	70	67
3.00	122	105	93	84	77	71	66	62	59	57
3.25	91	79	70	63	58	54	51	48	46	44
3.50	79	68	61	55	51	47	44	42	40	38
3.75	70	60	54	49	45	42	39	37	36	34
4.00	62	54	48	44	40	38	36	34	32	31

Sample size (donors) required for: 80% power, 2-sided type I error rate 5%. Continuity correction incorporated. Ψ=1.25 (where Ψ is a measure of the association between donors and their matched controls). Sample calculations done for a donor to control ratio of 1:10.

During the course of this thesis I recognized that this pilot study was "underpowered" to detect a clinically important effect, if it in truth exists (104). We were able to study only 55 donors matched to 502 controls. However the study was necessary to develop a future larger study.

CHAPTER 5- RESULTS

5.1. Selecting the Eligible Cohort

All the five datasets until March 31st, 2007 were reviewed at the Institute of Clinical Evaluative Sciences (ICES). The analysis was restricted to the first pregnancy after donation for donors. Sixty donors who became pregnant after donation from July 1991 to March 2007 were identified, and five were excluded. Four of the donors were hypertensive before 42 weeks prior to childbirth and one was diabetic. Thus, 55 donors were found eligible to be included in the analysis (Table 12).

Initially, 1,785,311 controls were identified and 212,990 were excluded. A larger proportion 79,176 (5%) of them were excluded because they were either too young (<20 years) or too old (≥50 years) to be included in the study. The next most frequently encountered complication among this group was hypertension. There were 61,530 (4%) of them who were excluded because they were diagnosed with hypertension prior to pregnancy. 53,000 (3%) were excluded since they had a diagnosis of diabetes mellitus, 9,416 (1%) kidney disease / glomerulonephritis, 8,847 (1%) systemic lupus erythematosus and 1,021 (0.5%) kidney failure requiring dialysis.

Table 12: Cohort Creation

Inclusion	**Donors**	**Unmatched Controls**
Number of childbirths (first childbirth after donation for donors only)	60	1,785,311
Exclusion* n (%)		
Kidney failure requiring dialysis	0 (0)	1,021 (0.5)
Diabetes Mellitus	1(2.0)	53,000 (3.0)
Hypertension	4 (7.0)	61,530 (4.0)
Kidney disease / Glomerulonephritis	n/a	9,416 (1.0)
Systemic Lupus Erythematosus	n/a	8,847 (1.0)
Age <20 or ≥50 at the time of childbirth	0	79,176 (5.0)
Numbers at end of cohort creation	**55**	**1,572,321**

*All exclusions were applied from July 1991 to 42 weeks prior to delivery

n/a: not applicable

5.2. Baseline Characteristics of Donors and Controls

5.2.1. Matched Controls to Donors

Donors were matched to non-donor controls. At least 10 controls per donor were identified for over 87% of the donors. As shown in Table 13, 48/55 (87.3%) donors were matched to 10 controls each. 1/55 (1.8%) donor was matched to six controls, 2/55 (3.6%) donors were matched to five controls, 1/55 (1.8%) to three controls and 3/55 (5.5%) to one control.

Table 13: Number of matched controls per donor

Number of donors	Number of controls for every donor	Percentage (%)
48	10	87.3
1	6	1.8
2	5	3.6
1	3	1.8
3	1	5.5

5.2.2. Baseline Characteristics, those used in Matching

The mean age of donors at the time of donation was 28 years (SD±5). As seen in Table 14, donors and non-donor controls were similar in most characteristics. The mean age was 32 (SD±5) at the time of delivery for both donors and non-donors. Majority of donor and non-donor control group (71%) were in the 30 to 39 age group at the time of childbirth. About a quarter of them (22-24%) were in the 20 to 29 age group and smaller percentages (5-7%) were in the 40 to 49 age group. For those who had previously given birth, the mean time since previous delivery was about eight years for donors and seven for non-donor controls. Among donors the mean time since donation and first childbirth was 4 (SD±3) years. Approximately 20 percent of the donors and controls were in the lowest

Table 14: Baseline characteristics of donors and controls (characteristics used for matching)

Characteristics	**Donors** (n = 55)	**Controls** (n=502)
Baseline		
Age at time of donation, years	28 (5)	n/a
Age at time of delivery, years	32 (5)	32 (5)
Age at time of delivery, years, categories, n (%)		
20 to 29.9	12 (22)	120 (24)
30 to 39.9	39 (71)	355 (71)
40 to 49.9	4 (7)	27 (5)
Time since last previous delivery, years	8 (4)	7 (3)
Time since donation, years	4 (3)	n/a
Income, lowest quintile for region, n (%)	11 (20)	105 (21)
Place of residence (urban), n (%)	53 (96)	463 (92)
During pregnancy		
Current multiple gestation	0	0

Mean (standard deviation) unless reported otherwise

n/a: not applicable

income quintile for the region. The majority of the donors and controls were urban dwellers. There were no multiple gestations reported among donors and controls.

5.2.3. Baseline Characteristic, those not used in Matching

Table 15: Baseline characteristics of donors and controls (characteristics not used for matching)

Characteristics	**Donors** (n = 55)	**Controls** (n=502)	**P-value‡**
Baseline			
Number of previous deliveries, categories, n (%)			
None	38 (70)	380 (76)	0.15
1	11 (20)	88 (18)	0.98
2 or more	6 (10)	34 (6)	0.72

‡ P-value calculated using Mantel-Haenszel chi- square test

The baseline characteristic of number of previous deliveries since July 1991 was not used in matching donors and non-donor controls. About 38/55 (70%) of donors and 380/502

(76%) of controls had no previous childbirth; 11/55 (20%) donors and 88/502 (18%) of controls had at least one child birth; 6/55 (10%) of the donors and 34/502 (6%) of controls had more than two previous childbirths. Significant differences between the two groups were calculated using the Mantel-Haenszel chi-square test, which accounts for matching in the analysis as discussed earlier. None of the differences was statistically significant for the characteristics tested. The formula used for the Mantel-Haenszel chi-square test is included in the Appendix.

5.3. Primary Outcome: Hypertensive Disorders of Pregnancy

The primary outcome of hypertensive disorders of pregnancy, was found to occur in 7/55 (13%) donors compared to 38/502 (8%) controls. As hypothesized, the point estimate of risk of developing a hypertensive disorder of pregnancy was higher after donation. Using generalised estimated equation, it was found that there was no statistically significant difference in hypertensive complications between donors and controls [13% vs. 8%, Odd's ratio (OR) 1.78, 95% confidence interval (CI) 0.75 – 4.19, p-value=0.19] (See Table 16). However, the wide confidence interval and statistically insignificant difference do not allow for any definite conclusion.

Table 16: Primary outcome: hypertensive disorders of pregnancy

	Number of events (%) of hypertensive complications of pregnancy	Odds ratio (95% confidence interval)	P Value
Control	38 / 502 (8%)	1.0 (referent)	
Donor	7 / 55 (13%)	1.78 (0.75 to 4.19)	0.19

5.4. Secondary Outcomes

As part of the secondary outcomes, individual components of the hypertensive disorders of pregnancy were analyzed. Due to privacy reasons, ICES does not provide counts between 1 and 5. There were ≤5 donors with gestational hypertension and preeclampsia. 21/502 (4.2%) controls had gestational hypertension and 6/502 (1%) had preeclampsia. There were no events of eclampsia, abruptio placenta, small for gestational age / intraute-

rine growth retardation and low birth weight / premature babies reported among donors. Counts were ≤5 among controls for abruptio placenta and low birth weight / premature babies. There were no events of eclampsia or small for gestation / intrauterine growth retardation among controls.

Table 17: Results of secondary outcomes

Events (%)	Donor (n=55)	Control (n=502)
Gestational hypertension	≤5* (≤1)	21 / 502 (4)
Preeclampsia	≤5* (≤1)	6 / 502 (1)
Eclampsia	0	0
Abruptio Placenta	0	≤5* (≤1)
Small for gestation / IUGR	0	0
Low birth weight / Prematurity	0	≤5* (≤1)

*Counts between 1 and 5 were not reported for reasons of privacy

5.5. Surveillance outcome

As noted earlier, a potential for information bias is that donors may have a more detailed follow up during pregnancy, which could result in more donors being diagnosed with pregnancy complications. To consider this potential source of bias, the number of antenatal visits was determined both for the donors and controls. Prenatal / antenatal visits were determined from CIHI diagnostic, OHIP diagnostic and procedural codes. As seen in Table 18, the number of health care visits to physicians did not differ between the two groups. The mean number of visits was 10 (SD±4) for donors and 9 (SD±4) for controls.

Table 18: Results of surveillance outcome

Events	Donor (n=55)	Control (n=502)
Number of health care visits [mean (SD)]	10 (4)	9 (4)

CHAPTER 6- DISCUSSION

In this study, it was found that donors do develop hypertension during pregnancy after donation. However, the sample size was too small to draw any firm conclusions about the degree to which this risk may be increased compared to controls. It is recognized that we need about 292 donors and 2920 controls (see Table 11: Sample size calculations) to detect a relative risk of 1.75, considering an event rate of 10% among controls. In this study, a relative risk of 1.78 was observed.

6.1. Summary of Results

Ontario health administrative data were used to assess pregnancy complications in living kidney donors. This pilot study provides some important information about the potential risk of hypertensive complications of pregnancy and major maternal and fetal adverse outcomes in the first pregnancy after donation, using an appropriate control group. An approximate two fold increase in the rate of hypertensive complications among donors in their first pregnancy after donation was observed when compared to matched controls from the general population (13% vs. 8%). However, the wide confidence interval and inadequate sample size does not permit any certain conclusions to be drawn. In theory it is possible that more diagnoses of hypertensive complications were made because blood pressure was monitored more carefully in donors compared to controls during their pregnancy. However, as demonstrated, donors and controls were seen by their physicians / health care provider, almost for the same number of antenatal visits. There were not adequate numbers of events reported on the secondary outcomes to make meaningful conclusions (gestational hypertension, preeclampsia, eclampsia, abruptio placentae, small for gestational age / intrauterine growth retardation, low birth weight / prematurity).

6.2. Strengths

This study has several strengths. First, the design and analysis is the most rigorous to date for the question posed. The study represents a strong feasible epidemiologic design, given that randomization to pregnancy or donation is not possible. Matching used in retrospective studies can effectively control for confounding. This method of selecting controls is probably the best method to assure that they were as healthy as donors. None of the previous studies have used this design. Comparing the first pregnancy after donation is also

useful. It is well known that the risk of hypertensive complication during pregnancy decreases with increasing parity.

To our knowledge, this is the first study done in Canada using administrative databases to examine the question posed. Follow-up through universal health records is almost perfect. Emigration from Ontario is very low and thus loss to follow up is minimal in the Ontario administrative data. Some previous studies have an average of 25% loss to follow up.

Validated codes with relatively high sensitivity and specificity were used for cohort identification and to assess outcomes. Codes were validated against either chart review or chart abstraction / recoding as reference standards.

Controls were selected with care, to avoid selection bias. Donors undergo a rigorous selection process and may be healthier than controls. Therefore, controls were matched to donors to appropriately reflect the excellent health status of donors. Moreover, they were also matched on important characteristics such as age at time of delivery.

This database study was conducted with ethics approval from the Sunnybrook Regional Ethics Board and the privacy impact of this study was considered both by the Ontario Trillium Gift of Life and the Institute for Clinical Evaluative Sciences (ICES) in Toronto.

6.3. Study Limitations

Several challenges merit discussion. Family history of preeclampsia, race and obesity are some of the risk factors for developing a hypertensive complication during pregnancy. These factors are unavailable in the administrative data and therefore donors and controls could not be matched on these characteristics. However, six important prognostic characteristics that were available in the database were used in the matching. (Age within one year at time of pregnancy, year and quarter of cohort entry date and last previous delivery, history of previous pregnancy with hypertensive complications, multiple gestation in the current pregnancy and socio economic status based on neighbourhood income quintile).

The population level datasets used in this study lack renal function test values, blood pressure measurements and lifestyle measures. Conversely, many other variables were accurately recorded including a range of diagnoses, physician visits, hospitalizations and co-morbidities. The variables were ascertained using codes, which accurately represented information typically found in a patient's medical record.

Donors in general may be more health conscious and therefore would have had excellent health before pregnancy. The extent of health care utilization by the donors and non-donor controls was not matched in the study.

There were a finite number of donors available in the data. This study had less than 80% statistical power to detect smaller risks in the primary outcome should it in truth exist. Nonetheless, the current study presented a valuable opportunity to extend knowledge. It lays the foundation for a future update with a larger number of pregnant donors.

Limitations of Ontario's health administrative database are recognized. Many of the data-sets are only reliable after the year 1990, restricting the timeframe to a start date of July 1991. However, this is less of a concern as the popularization of living donation has only really occurred in the last two decades.
Finally, over 92% of the population of Ontario is Caucasian. Thus the results may generalize less well to non Caucasian living kidney donors.

CHAPTER 7- FUTURE RESEARCH AND CONCLUSIONS

7.1. How Donors should be Cared for?

Given the new results and the remaining uncertainty, how should female donors be counselled and cared for? All existing data reassures us that donation poses no great harm to pregnancy. However, the total number of hypertensive disorders of pregnancy events across all studies remains low, and the studies suffer from limitations, as previously described.

The effects of donation on maternal and fetal outcomes should be discussed with potential donors and their recipients. There may be a greater chance of developing hypertension which may manifest during pregnancy, or even giving birth to a premature baby, than would occur otherwise. It remains prudent to monitor the pregnancies of kidney donors. In practice it is recommended that women with uncomplicated pregnancies be examined every 4 weeks until 28 weeks of gestation, every 2-3 weeks until 36 weeks, and weekly thereafter until delivery (109). These examinations include the monitoring of urine protein and blood pressure at every visit. Fetal ultrasounds are recommended at least once between 18 and 22 weeks gestation to assess the development of the fetus during routine antenatal care. Thus, a reasonable emphasis for the care of living kidney donors is adherence to the high level of surveillance and monitoring recommended for all pregnant women. While there is no clear evidence to guide the timing of pregnancies after donation, planning to delay pregnancy at least a year after nephrectomy seems reasonable to allow a woman to recover from the emotional process of becoming a living donor and to adapt to her new level of renal function.

7.2. An Agenda for Future Research

Looking ahead, this pilot study will be updated by adding additional years of recruitment and follow-up. The next update should include at least 180 women in their first pregnancy after kidney donation, which can be achieved by waiting a few more years and by cleaning of existing Trillium Gift of Life data. In The Trillium dataset 2033 individuals had a donor nephrectomy between July 1, 1993 and March 31, 2005. It was expected ~10% of the donors would not be linked to Ontario administrative data because they came from out of province. However, there was a large amount of missing information on

health card numbers and patient demographics in the Trillium dataset (~40%). Fortunately, donor nephrectomy is a surgical procedure that is well recorded in hospital medical charts. Thus a student will be hired at each of the seven transplant centers in Ontario to review the hospital charts and to fill in missing fields in the Trillium data.

In addition to the matching variables used in this study, matching on the number of previous pregnancies will make the controls and donors as comparable as possible. However this approach will only account for pregnancies after 1991, as this is the beginning of the dataset. Other secondary outcomes such as maternal and neonatal death are also of interest. Any increase in the number of stillborns could be included among other secondary outcomes.

Ultimately, a rigorously conducted prospective cohort study with similar groups of donors and non-donor controls remains the best way to accurately estimate the risk of adverse maternal and fetal outcomes. Reporting counts and risk ratios for subgroups defined by maternal age, previous uncomplicated obstetrical history, and time since donation may help provide advice tailored to the needs of individual donors. Conducting such a study has the challenge of recruiting female donors and controls across multiple transplant centres and retaining participants in follow-up for years after donation. Many more female donors and controls will need data recorded prior to the donation process, to later enroll an estimated 200 donors and 200 controls who then become pregnant. These efforts will help rule out a twofold or greater increase in the risk of hypertensive disorder of pregnancy after donation, if such a risk truly exist. While such a 10-year multi-centre prospective cohort study could be used to follow donors and controls for pregnancies after donation, the cost, logistical considerations and timeliness may prove prohibitive.

7.3. Conclusion

This study directly aimed to understand maternal and child health outcomes using anonymised health data. By accepting healthy persons into the role of a donor, our health care system takes on additional responsibility beyond our 'normal' tasks of curing, or at least helping patients with a disease (110). Living kidney donation is a unique model to help clarify the role of the kidney and reduced nephron mass in the development of

hypertensive disorders of pregnancy. From a clinical perspective, the information gained from this study and further research will help improve donor selection, informed consent and best practices which follow donors for long term good health.

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APPENDICES

Appendix A: Data Creation Plan (submitted to ICES)

The Risk of Hypertensive Disorders in Pregnancy after Living Kidney Donation

Study Number	2006 0622 020 000
PI and P&B Contacts	Amit Garg: amit.garg@lhsc.on.ca (519) 685-8502 Immaculate Nevis: immaculate.nevis@lhsc.on.ca (student) (519) 685-8500 x 55981
PIA Approved	Yes
Date last modified and by whom	July 11, 2008 Immaculate Nevis
Short description of research question	To determine whether living kidney donors are at higher risk of developing hypertensive complications of pregnancy (preeclampsia, eclampsia, PIH) than comparable non-donors
List of Datasets Used	CIHI, OHIP, TGLN, ODD, RPDB

Defining the Cohort

Two Groups of Matched Cohort

Exposed individuals: female living kidney donors identified by multiple data sources who are at least 20 weeks pregnant.

Background of donors dataset

Use method to identify kidney donors defined in: Study 2006 0622 010 000, "The Risk of Premature Cardiovascular Disease after Living Kidney Donation".
CIHI or OHIP Databases ("Pings Cohort")
ICD-9: V594 and CCP: 67.41 or 67.5; or ICD-10: Z524 and CCI: 1PC58; or OHIP fee code: E753

This dataset was used to help making linkage of TGLN

1. Trillium Gift of Life Network Donor Database
2. Trillium Gift of Life Network Recipient Database
3. Age $\leq$ 50 at the time of donation for this study

Excluded any recipients (at any time) from those identified as donors [Note: A very low number of donors may have gone on to develop kidney failure after donation- in this analysis we have excluded such individuals]

Non-exposed individuals (controls): Females from the general population (use RPDB) who are at least 20 weeks pregnant;

1. Have never donated a kidney or had a nephrectomy between July 1991 and March 2007 (none of any of these codes) ICD-9:V594,V598,V599, CCP: 67.3, 67.4, 67.5; **ICD-10**: Z524; **CCI:** 1PC58; **OHIP fee code**: S411, S412, S413, S415, S416, S420, S436, E753, E763, E766, E767, E768, E769, E771;
2. Not listed in Trillium data file as donor or recipient

Primary outcome
Incidence of first hypertensive complication of pregnancy (see definition in outcomes section)

Cohort Entry
Date of cohort entry/patient identification: Date of the **first** of the following codes related to delivery of fetus as identified in CIHI and OHIP databases. Any code that is dated within 6 months of the date of the first code will be considered the same delivery.

For donors only first delivery after donation is considered, but for controls multiple deliveries (6 month role) to maximize the number of controls.

It is necessary to identify women who carried their pregnancy to at least 20 weeks gestation as our primary outcome cannot develop until after 20 weeks gestation.

1. Normal vaginal delivery: **ICD-9**: 650 [Normal delivery]; **CCP**: 87.98 [Delivery NEC]; **ICD-10**: O80 [Single spontaneous delivery], O75701, O75703, O75709 [Vaginal delivery following previous caesarean section]; **CCI**: 5MD50 [Manually assisted vaginal delivery], 5MD51 [Spontaneous vaginal delivery], 5MD52 [Water birth]; **OHIP DxCode**: 650 [Normal delivery, uncomplicated pregnancy]; **OHIP fee code**: P006 [Vaginal delivery], P010 [Attending obstetrician consultant at delivery] , P011 [Attending at labour and delivery by a physician other than obstetric. consult];
2. Caesarean section: **ICD-9**: 6697 [Caesarean delivery]; **CCP**: 86.0 [Classical caesarean section], 86.1 [Cervical caesarean section], 86.2 [Extraperitoneal caesarean section], 86.8 [Caesarean section of other specified type], 86.9 [Caesarean section of unspecified type]; **ICD-10**: O82 [Single delivery by caesarean section]; **CCI**: 5MD60 [Caesarean section]; **OHIP fee code**: P018 [Caesarean section], P041 [Caesarean section incl. tubal interruption] , P042 [Caesarean section incl. hysterectomy];
3. Breech delivery: **ICD-9**: 6696 [Breech extraction]; **CCP**: 84.5, 84.6 [Breech extraction]; **ICD-10**: O32101 [Maternal care for breech presentation, delivered]; **CCI**: 5MD56 [Breech delivery];
4. Malpresentation at delivery: **ICD-10**: O32201 [Maternal care for transverse and oblique presentation, delivered], O32301 [Maternal care for face, brow, chin presentation, delivered], O32401 [Maternal care for high head, delivered], O32501 [Maternal care for multiple gestation with malpresentation, delivered], O32601 [Maternal care for compound presentation, delivered], O32801, O32901 [Maternal care for other malpresentation, delivered]
5. Operational delivery other than caesarean section (forceps delivery, vacuum extraction): **ICD-9**: 6695 [Forceps delivery]; **CCP** 84.0, 84.1, 84.2, 84.3, 84.4, [Forceps delivery], 84.7, [Vacuum extraction], 84.8, 84.9 [Other instrumental delivery]; **ICD-10**: O81 [Single delivery by forceps or vacuum extraction]; **CCI**: 5MD53 [Forceps traction and rotation delivery], 5MD54 [Vacuum traction delivery], 5MD55 [Combination of forceps and vacuum]; **OHIP fee code**: P020 [Operational delivery other than caesarean section];

6. Pre-term delivery: **ICD-9**: 6442 [Early onset delivery]; **ICD-10**: O60 [Preterm delivery], O75801, O75802, O75803, O75804, O75809 [Preterm labour with delivery delayed by therapy];
7. Post-term delivery: **ICD-10**: O48 [Prolonged pregnancy]
8. Single birth: **ICD-9**: V270 [Deliver-single live born], V271 [Deliver-single still born]; **ICD-10**: Z370 [Single live birth], Z371 [Single stillbirth];
9. Multiple births: **ICD-9**: V272, V273, V274 [Deliver-twins], V275, V276, V277 [Deliver-multiple birth]; **ICD-10**: O84 [Multiple delivery], O30001 [Twin pregnancy delivered], O30101 [Triplet pregnancy delivered], O30201 [Quadruplet pregnancy delivered], O30801 [Other multiple gestation delivered], O30901 [Multiple gestation unspecified, delivered] Z372, Z373, Z374 [Twins], Z3750 [Triplets, all live birth], Z3751 [Quadruplets, all live birth], Z3752 [Quintuplets, all live birth], Z3753 [Sextuplets, all live birth], Z3758, Z3759 [Other multiple birth, all live], Z3760, Z3761, Z3762, Z3763, Z3768, Z3769 [Multiple births, some live born], Z3770, Z3771, Z3772, Z3773, Z3778, Z3779 [Multiple births, all stillborn], Z3790 [Multiple birth, unspecified];

NOTE: We realize that ICD9 codes are not available for #4 and #7. Since #4 and #7 was an additional way of finding the cohort, as most of deliveries would be picked up by normal vaginal/caesarean section codes. This would not affect the study in any way.

Exclusion Criteria

Exclusion criteria for both donors and controls (In order)

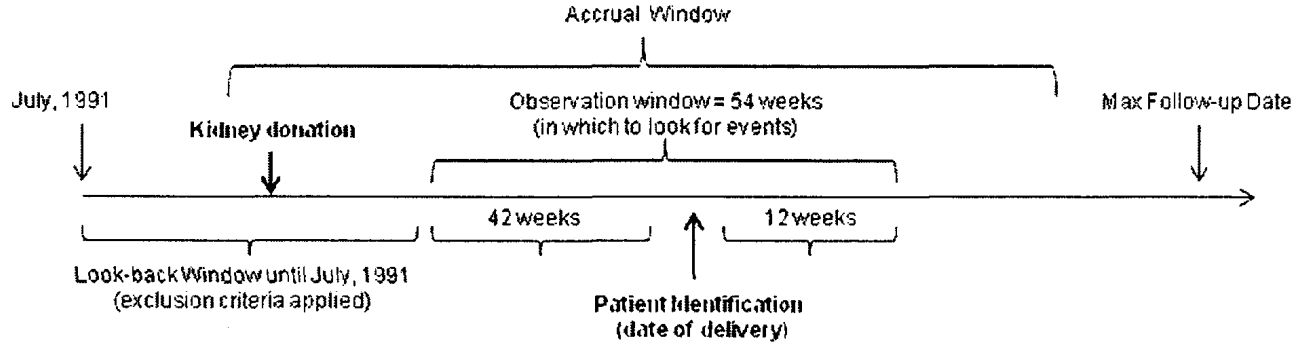
Evidence of any of the following more than 42 weeks prior to the time of patient identified as delivering fetus. *[Pregnancy is not allowed to continue past 42 week, labour is induced between 40 and 42 weeks gestation]*

1. Kidney failure receiving dialysis: **CCP**: 5195 [Hemodialysis], 6698 [Peritoneal dialysis]; **CCI**: 1PZ21 [Dialysis, urinary system]; **OHIP fee code:** R849 [Dialysis initial and acute], G082,G083,G085,G090,G091,G092,G094,G095,G096 [Continuous HD] ,G294,G295 [Ultra filtration],G323,G325,G326 [Hemodialysis] ,G330, G331, G332 [Peritoneal dialysis], G333 [Home/self care dialysis], G860 [Hemodialysis – hospital location], G861 [Peritoneal dialysis – hospital location], G862 [Hospital self care dialysis], G863, G864, G865, G866 [Dialysis unspecified];
   Explanation: to ensure that no kidney recipients were accidentally coded as donors
2. Diabetes mellitus via ODD
3. Hypertension: Presence of a code for hypertension in CIHI **ICD-9**: 401x-405x in any of the 16 diagnostic fields; **ICD-10**: I10-I13, I15 in any of the 16 diagnostic fields; Presence of at least two OHIP DxCodes for hypertension in OHIP **OHIP DxCodes:** 401, 402, 403
   Note: may notice a fair number of donors are excluded from analysis as a result of these exclusion criteria, but is important to exclude them as both diabetes and hypertension are risk factors for the primary outcome.

Exclusion criteria for controls only (In order)

4. Kidney disease/Glomerulonephritis: **ICD-9**: 581 [Nephrotic syndrome], 582 [Chronic proliferative nephritis], 583 [Nephritis], 584 [Acute renal failure], 585 [Chronic renal failure], 586 [Renal Failure], 587 [Renal Sclerosis NOS], 588 [Impaired renal function], 7885 [Oliguria and anuria], 753 [Renal Agenesis], 403 [Malignant hypertension with renal disease], 405 [Malignant reno-vascular hypertension], 593 [Nephroptosis]; **ICD-10**: N17 [Acute renal failure], N18 [Chronic renal failure], N19 [Renal failure, unspecified], N01 [Rapidly progressive nephritic syndrome], N03 [Chronic nephritis], N25 [Diffuse mesangio capillary necrosis], NO52 [Unspecified nephritic syndrome], N053-55 [Unspecified nephritic syndrome], NO72-74 [Hereditary nephropathy; Glomerulonephritis], I12 [Hypertensive renal disease], I13 [Hypertensive heart and renal disease], R34 [Oliguria and Anuria]; **OHIP DxCodes**: 580 [Acute Glomerulonephritis], 581 [Nephrotic syndrome], 584 [Acute renal failure], 585 [Chronic renal failure, uremia];
5. Systemic Lupus Erythematosus: **OHIP DxCodes**: 710;

Time Frame Definitions



Accrual Start/End Dates	July 1993 to December 31, 2006
Max Follow-up Date	March 31, 2007
When does observation window terminate for the analysis of any given outcome?	The first of the following dates (in order): • Date of event (date of occurrence of outcome of interest • 12 weeks after patient date of delivery (date of identification/cohort entry) • March 31, 2007
Period of Outcome Assessment	Look between 42 weeks before patient identification to 12 weeks after
Look-back Window	July, 1991

Variable Definitions

Main Exposure or Risk Factor: Exposure is living kidney donation

Baseline Characteristics

These variables will be used in the first table that compares donors to controls on their baseline characteristics. It describes the baseline health status of the two groups.

At the time of patient identification (cohort entry)

1. Age
2. Residency (Rural versus Urban – for table 1)
3. Income based socioeconomic status (income quintiles)
4. Year and quarter of date of delivery/cohort entry
5. Any previous pregnancies with hypertensive complications of pregnancy (use same definition for hypertensive complication or pregnancy as in primary outcome)
6. Number of previous pregnancies since July1991 (use definition of pregnancy for cohort entry)
7. Year and quarter of date of last pregnancy

8. Current multiple pregnancies (ie: number of multiple gestations in pregnancy of cohort entry; use codes for multiple gestation from cohort entry) - *We do not expect this to differ between groups*

Other

1. Donor race (TGLN variable DON_RACE)
2. Donor relationship to recipient (TGLN variable LDON_RELATIONSHIP_CODE)
3. Age at time of donation
4. Year and quarter of donation
5. Years since donation

Matching Variables

Aim to match 10 controls for every donor, if not possible match as many as possible

1. Birth date (within 1 year)
   Age (very young and older mothers) is a risk factor for hypertensive complications of pregnancy
2. Income quintiles at the time of cohort entry
   To control for SES
3. Cohort entry date (ie: date of delivery; within 3 months)
   Can increase to 6 months if matching is difficult
4. Date of last pregnancy (within 6 months)
5. Any previous pregnancy with hypertensive complications – use hypertensive complication of pregnancy definition for primary outcome)
6. Current multiple gestations (ie: in pregnancy of cohort entry) – use multiple births codes from primary outcome definition
   Multiple gestation is a risk factor for hypertensive complications of pregnancy

Outcome Definitions

Primary Outcome

Explanation: with respect to significance testing, this outcome will be considered the primary test used in hypothesis testing, with a two-tailed p value <0.05 considered significant; because of our exclusion and matching criteria, no adjustment will be required.

- **Hypertensive complications of pregnancy** (evidence of the first of any of the following events between 42 weeks before cohort entry and 12 weeks after)
  - Gestational Hypertension: **ICD-9**: 6429 [Hypertension during pregnancy]; **ICD-10**: O13001-O13004, O13009 [Gestational hypertension without proteinuria]
  - Preeclampsia: **ICD-9**: 6424 [Mild preeclampsia], 6425 [Severe preeclampsia]; **ICD-10**: O14001-O14004, O14009 [Gestational hypertension with significant proteinuria]
  - Eclampsia: **ICD-9**: 6426 [Eclampsia]; **ICD-10**: O15001, O15003 [Eclampsia in pregnancy], O15101, O15103 [Eclampsia in labour], O15201, O15203

[Eclampsia in the puerperium], O15209 [Eclampsia unspecified]; **OHIP DxCode**: 642 [Preeclampsia, eclampsia, toxaemia];

Secondary Outcome

- Preeclampsia: **ICD-9**: 6424 [Mild preeclampsia], 6425 [Severe preeclampsia]; **ICD-10**: O14001-O14004, O14009 [Gestational hypertension with significant proteinuria]
- Eclampsia: **ICD-9**: 6426 [Eclampsia]; **ICD-10**: O15001, O15003 [Eclampsia in pregnancy], O15101, O15103 [Eclampsia in labour], O15201, O15203 [Eclampsia in the puerperium], O15209 [Eclampsia unspecified];
  Note: OHIP DxCode 642 was intentionally omitted from the definition of eclampsia for secondary outcome analysis as it does not distinguish between preeclampsia and eclampsia
- Gestational Hypertension: **ICD-9**: 6429 [Hypertension during pregnancy]; **ICD-10**: O13001-O13004, O13009 [Gestational hypertension without proteinuria];
- Abruptio placentae: **ICD-9**: 6412 [Prem separ placen], **ICD-10**: O45 [Premature separation of placenta –abruptio placentae],
- Small for gestational age (SGA), intrauterine growth restriction (IUGR): **ICD-9**: 6565 [Poor fetal growth], 7649 [Fetal growth retardation], 7640-7641 [Light for dates], **ICD-10**: P0590 [Symmetric Intra-uterine growth retardation[IUGR]], P0591 [Asymmetric intra-uterine growth retardation [IUGR]], P0599 [Unspecified intra-uterine growth retardation [IUGR]];
- Prematurity, Low birth weight (LBW): **ICD-9**: 7650 [Extreme immaturity], 7651 [Other preterm infants] **ICD-10:** PO70 [Extremely low birth weight], PO71 [Other low birth weight], PO72 [Extreme immaturity] PO73 [Other preterm infants] **OHIP DxCode**: 765 [Prematurity, low birth weight infant];

Descriptive Outcome

- Gestational Diabetes: ICD-9: 6480 [Diabetes in pregnancy]; ICD-10: 024 [Diabetes mellitus in pregnancy]
  [This outcome is for interest only, and to inform future studies]

Surveillance Outcome

- Number of prenatal or antenatal visits per patient in the 42 weeks before cohort entry – A single prenatal or antenatal visit is defined as the presence of one or more of the following codes on **a single day**: **ICD-9**: V220, V221 [Supervision

normal pregnancy], V230 [Pregnancy with history of infertility], V231 [Pregnancy with history of trophoblastic disease], V232 [Pregnancy with history of abortion], V233 [Grand multiparity], V234 [Pregnancy with poor obstetric history], V235 [Pregnancy with poor reproductive history], V238, V239 [Supervision of high risk pregnancy],V288, V289 [Antenatal screening]; **CCP**: 02.88 [Diagnostic ultrasound of gravid uterus]; **ICD10**: Z34 [Supervision of normal pregnancy], Z35 [Supervision of high risk pregnancy] **CCI**: 5AB01 [Antepartum care], 5AB03 [Obstetrical ultrasound investigations]; **OHIP DxCode**: 970 [Prenatal care]; **OHIP fee code**: P003 [Prenatal care, general assessment, major visit], P004 [Minor assessment, all other prenatal visits], P005 [Prenatal care, Antenatal preventative health assessment];

Appendix B:

Formulas Used for Calculation of p-value for Baseline Characteristics

The Mantel Haenszel Chi-square test is defined as:

$\chi^2_{MH} = [\Sigma_k(a_k - m_{1k}*n_{1k}/n_k)] / [\Sigma_k \{m_{1k}*m_{2k}*n_{1k}*n_{2k}/n_k^2(n_k-1)\}]$,
where a_k, m_{1k}, n_{1k} and n_k are defined by the entries in the k'th table

	donors	controls	
Yes	a_k	b_k	n_{1k}
no	c_k	d_k	n_{2k}
	m_{1k}	m_{2k}	n_k

Formula used for sample size calculation

This follows the method given by Fleiss, Levin and Paik (2003) on pages 394-398, and is initially based on the use of McNemar's test.

Let 'm' be the number of discordant pairs; the computation of the required m has two steps

$m_1 = \{z_{\alpha/2}(1+\omega) + 2 z_\beta(\sqrt{\omega})\}^2 / (\omega-1)^2$
where $\omega = p / (1-p)$ and p is the probability of experiencing the event (hypertension in pregnancy) among the controls under the alternative hypothesis. The value of p under the null is 0.5.
Next we adjust for continuity, that is, for the fact that we are using a continuous distribution, the Normal, to calculate values for a discrete distribution.

$m = m_1/4 (1+ \sqrt{1+[4(\omega+1)] / [m_1(\omega-1]}})^2$

If p_d is the probability of discordance, then M, the required number of pairs is m/ p_d

This provides the required sample size for matched pairs. For 1: r matching, that is 1 case for r controls, the required sample size is [(r+1)/2r] M (where r = 10 in this study). In this case the appropriate procedure is the Mantel-Haenszel test.

Fleiss, J.L., Levin, B. and Paik, M.C. (2003). Statistical Methods of Rates and Proportions. 3rd edition. Wiley: Hoboken, New Jersey

Appendix C: Identifying the Study Team

In the year 2002, the DONOR (Donor Nephrectomy Outcomes Research) Network was established, to generate new knowledge to improve the practice of living kidney donation. The network has representation from every major transplant centre in Canada. Many of the investigators are nephrologists or surgeons who care for living kidney donors, and completed formal graduate training in clinical epidemiology or health services research, translational research and economics. They are joined by experts with doctoral degrees in health policy, qualitative research, pschycological assessment, economics and biostatistics. Investigators in the Network actively discuss science and feasibility. In 2008, an annual CIHR funded conference in Philadelphia, USA was held, and the future projects on this topic were discussed in detail. Within this project, my duties included generation of research question, developing the protocol / data creation plan, reviewing literature background, synthesis and analysis of study results.

Ms. Meghan Vlasschaert M.Sc: Ms. Vlasschaert has a master's degree in epidemiology and biostatistics and her research interest is on validation of codes in renal administrative databases. Her master's thesis was in "The accuracy of renal codes within health administrative data: A systematic review." Her comments and insights on the data creation plan were helpful in conducting this project.

Dr. Ping Li PhD: Dr. Li is a senior analyst at ICES (Institute of Clinical Evaluative Sciences) Toronto. Only certain individuals are permitted access to the databases. Dr. Li programmed and provided the outputs for my data creation plan.