Living donor transplantation

– *outcome and risk*

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Gothenburg, Sweden, 2017

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ISBN 978-91-629-0177-6

Printed in Gothenburg, Sweden 2017
Ineko AB

To all live organ donors

Abstract

Live organ donors undergo extensive surgery to provide an organ that can be lifesaving or improve the health and quality of life for the recipient. The thesis seeks important knowledge that may be used to further reduce the donor risk for the live kidney donor as well as for an entirely new group of living donors, the uterus donor. The general aims were to investigate the outcome for the living kidney and uterus donor in both organ specific measurements and quality of life in the recovery after donation, as well as to investigate if there are markers indicating elevated risk for the donor.

Living kidney donors at the Department of Transplantation Surgery at the Sahlgrenska Academy, Sahlgrenska University Hospital and the live uterus donors at the Department of Obstetrics and Gynaecology at the Sahlgrenska Academy, Sahlgrenska University Hospital, were recruited. The study types used herein included a cross-sectional study on long-term kidney function, analysis of internal quality register data and prospective studies on both living kidney and uterus donors. Both objective and quantified subjective data (Patient-Reported Outcome) were used for statistical analysis. After an initial decrease, followed by the removal of one kidney at donation, the kidney function increased over time after donation for years while later on it decreased with donor age. The number of arteries did not seem to affect the initial increasing capacity of the remaining kidney. The kidney donor was typically recovered both physically and mentally after three months following donation and socioeconomic factors may have influenced the recovery. The entirely new donor group, living uterus donors, returned to their previous physical health and well-being after the donation.

In conclusion, implementation of the current guidelines on living donor evaluation and care provides safe selection and minimize the donor risk although psychosocial and socioeconomic factors may influence the recovery.

Keywords

living donor, kidney, uterus, transplantation, surgical complications, recovery

Sammanfattning på svenska

Den bästa behandlingen för njursvikt i slutstadiet är transplantation. Det råder brist på njurar från avlidna givare för transplantation. Njurar används därför från levande givare (donatorer) med utmärkta resultat både för givaren och mottagaren sedan 1964 i Sverige. Resultaten för mottagaren är bättre med njure från levande givare än från avliden. Säkerheten för de levande givarna av största vikt då de inte har någon vinning för den egna hälsan och genomgår ett stort ingrepp i bukhålan som innebär borttagande av ena njuren. Under senare år har man forskat på livmoderstransplantation för att behandla infertilitet (ofruktsamhet) som är orsakat av avsaknad av livmoder eller annan störning i livmoderns funktion. Denna form av infertilitet kan inte botas eller behandlas på annat sätt idag. På Sahlgrenska Universitetssjukhuset genomfördes världens första serie med livmoderstransplantation med levande givare.

Denna avhandling innehåller fyra delarbeten som syftar till att belysa hur det gick både för njurdonatorna och den helt nya gruppen av donatorer, livmodersdonatorerna, efter operationen. Den första studien avsåg att undersöka hur njurfunktionen utvecklades på lång sikt hos levande njurdonatorer genom en tvärsnittsstudie. Studie två mätte om det var skillnad på resultat sex månader efter donationen mellan donatorer med ett eller flera blodkärl till den kvarvarande njuren. Studie tre och fyra avsåg att undersöka hur återhämtningen var både fysiskt och psykiskt efter njurdonationsoperationen respektive livmodersdonationsoperationen. För att mäta återhämtningsprocessen användes både objektiva och subjektiva (självupplevda) markörer. Subjektiva mått på hälsan inhämtades genom att donatorn fyllde i hälsoenkäter där svaren sedan översattes till en summa.

Det visade sig att njurfunktionen fortfarande återhämtade sig över 10 år efter njurdonationen efter att den halverats genom borttagandet av den ena njuren. En stor del av återhämtningen skedde inom det första halvåret (från 50% till 70% av ursprungsnivån) och den verkade inte påverkas av att den kvarstående njuren hade avvikande blodförsörjning i form av flera separata pulsådror. Den fysiska och psykiska återhämtningen tog tre månader från njurdonationen och alla återhämtade sig efter livmoderdonationen. Donation med njure och livmoder verkar säkert med den nuvarande noggranna utredningen inför ingreppet.

List of papers

The thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Fehrman-Ekholm I., **Kvarnström N.**, Söfteland J., Lennerling A., Rizell M., Odén A., Simonsson T.

Post-nephrectomy development of renal function in living kidney donors: a cross-sectional retrospective study.

Nephrology Dialysis Transplantation 2011; 26: 2377–2381.

II. **Kvarnström N.,** Fehrman-Ekholm I., Olausson M., Lennerling A.

Is there an increased risk for hypertension or worse outcome in live kidney donors left with multiple (>1) renal arteries?

Submitted manuscript.

III. **Kvarnström N.,** Fehrman-Ekholm I., Söfteland J., Olausson M., Lennerling A.

A prospective study on recovery after living kidney donation.

Submitted manuscript.

IV. **Kvarnström N.,** Järvholm S., Johannesson L., Dahm-Kähler P., Olausson M., Brännström M.

Live Donors of the Initial Observational Study of Uterus Transplantation—Psychological and Medical Follow-Up Until 1 Year After Surgery in the 9 Cases.

Transplantation 2017; 101: 664 -670.

Content

Abbreviations

CID	Clinical Important Difference
CT	Computed Tomography
CTA	Composite Tissue Allograft
DAS	Dyadic Adjustment Scale
DVT	Deep Vein Thrombosis
eGFR	Estimated Glomerular Filtration Rate
ESRD	End Stage Renal Disease
FDA	Food and Drug Administration
FIGO	International Federation of Gynecology and Obstetrics
FSGS	Focal and Segmental Glomerulosclerosis
GFR	Glomerular Filtration Rate
GODT	Global Observatory on Donation and Transplantation
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale Anxiety
HADS-D	Hospital Anxiety and Depression Scale Depression
Hb	Haemoglobin
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
MCAR	Missing Completely at Random
MCS	Mental Component Summary score
MDRD	The Modification of Diet in Renal Disease
mGFR	Measured Glomerular Filtration Rate
MRA	Magnetic Resonance Angiograms
MRI	Magnetic Resonance Imaging
OPTN	Organ Procurement and Transplantation Network
PCS	Physical Component Summary score
PGWB	Psychological General Well-Being Index
PRO	Patient Reported Outcome
PRP	Post-Operative Recovery Profile
PTH	Parathyroid Hormone
QoL	Quality of Life
SD	Standard Deviation
SF-36	Short Form 36

1. Introduction

1.1 Background of organ transplantation

The first successful kidney transplantation between homozygous twins was performed by Joseph Murray in 1954 (1). However, in implementing organ transplantation as a potential treatment for end stage organ failure for all patients other than homozygous twins, several important discoveries were needed. The history of finding of the human leucocyte antigens (HLA) that are used today for tissue matching has been described by Erik Thorsby and important contributions to that research were made in Gothenburg by Lena Sandberg (2). That discovery and the introduction of new immunosuppressive drugs, first azathioprine (3) and then the calcineurin inhibitors cyclosporine (4) and FK-506 (tacrolimus) (5), have made clinical organ transplantation possible. After the first kidney transplantation, other lifesaving organs were successfully transplanted during the next decades; liver (6), heart (7), lung (8), pancreas (9), intestine (10), multiple abdominal viscera (11), and bone marrow (12).

Clinical successful transplantations with composite tissue allograft (CTA) such as hand CTA (13) begun in 1999 after promising studies on animals with the use of the new immunosuppressive drug mycophenolic acid (14) in combination with calcineurin inhibitors (15, 16). After five years of observation on the hand CTA results and after ethical discussions, the group in Lyon led by Dubernard perform the first face CTA in 2005 (17). The first uterine CTA were performed in 2000 by Fageeh and co-workers (18) and until today 21 cases have been published including the nine cases in the clinical trial at Sahlgrenska University Hospital in 2012-2013 (19-23). The trial was performed following extensive ethical discussions (24, 25) and experimental animal studies (26-28) to optimize the procedure.

1.1.1. Organ shortage –the need for living donors

Transplantation is the only treatment for end stage failure of organs such as heart and liver and is the best treatment for end stage kidney decease with regards to quality of life (QoL), cost effectiveness and survival (29, 30). Since 2010 the demand for organs has increased more than the deceased donor rate in the Nor-

dic countries, resulting in added patients on the waiting list and the need for kidneys from live donors is thereby not diminished (31). The number of kidneys from live donors in Sweden increased during the first four decades following the first transplantations performed in 1964, reaching a level of about 150 per year in 2004 and forward, with an all-time high in year 2011 with 184 procedures (32). As the situation is similar in the rest of the countries within the European Union, the European Commission released a policy document in 2007 to support organ donation from both living and deceased donors (33).

1.2 Live donor versus deceased donor

In order to assess the suitability of choosing a live donor instead of a deceased donor there are various aspects that have to be considered. The type of organ also limits the potential for safe living donation. The kidney is the most frequently used organ for living donation according to the databases provided by the Organ Procurement and Transplantation Network (OPTN) and the Global Observatory on Donation and Transplantation (GODT) accessed on February the 24th 2017 (34, 35). Other vital organs such as the liver, the pancreas and the bowel can only be partially donated as they are not paired, and the organ needs to be transected in a live donor while they can be donated as whole organ by a deceased donor (36). The lungs are paired organs but normally only one of the lower lobes are donated by a live donor (37). The uterus is not a vital organ, hence the uterine donors are not at risk of sustaining life threatening complications related to the lack of the organ itself (38).

1.2.1 Ethical considerations

Living organ donation implies a conflict between two different basic medical ethical principles: the principle of net benefit and principle to respect autonomy (39). The principle of net beneficiary for the patient originates from the Hippocratic Oath: *primum non nocere*. That means that a surgical procedure although maleficence in some respects should be ultimately beneficial for the patients' health. In living organ donation, the donor does not benefit medically from the surgery however there may be other beneficial aspects when improving the health of a close friend or a family member. Nevertheless, that does not apply in non-directed donation when the recipient is anonymous to the donor. To approve of the decision to donate is to respect the donors' autonomy. To assess the underlying risk for the donation procedure itself together with recipients' expected

health benefit, is a major aspect when deciding if the donation is ethically correct or not as discussed by Bonomini and Guzzetti in 1990 (40). In order to guide the medical professionals involved in the care for the donor an important consensus regarding the ethics of living donation has been formed. In the consensus statement of the Amsterdam forum 2004, there is agreement on how to minimize the physical, social and psychological risk for the living kidney donor (41). Furthermore, the statement outlines the importance of a fully informed consent and minimizing the effect of coercion as the decision to donate should be entirely voluntary. In 2006, similar guidelines for the live donation of liver, lung, pancreas, and bowel was published from Vancouver (42). There has also been formed a consensus against organ trafficking and transplant tourism in the Istanbul declaration of 2008 which seeks to prevent potential donors from being taken advantage of by another party. The aim was to preclude any coercion from another party that takes advantage of unequal power in relation to the donor. That includes any monetary transaction that exceeds reimbursement for costs related to the donation (43).

The basic ethical premises in organ transplantation as outlined above can be applied to the living uterus donor although uterus transplantation is still in the study phase. However, as both the true benefit and maleficence were unknown and because uterus transplantation is not a lifesaving procedure, the International Federation of Gynecology and Obstetrics (FIGO) committee in 2009 stated that living donor uterus transplantation was ethically inappropriate (44). Large animal models including primates, as well as hysterectomies on humans with vascular grafting have subsequently provided knowledge and the ethical concerns have been further debated (26, 27, 45, 46). The research on uterus transplantation lead by Professor Brännström in Gothenburg had followed the principles of ethical analysis of surgical innovations as described by Moore; laboratory background, field strength and institutional stability (27, 47) and the IDEAL concept for new surgical therapies (48). With important contributions from Professor Olausson, the point was reached where only a study on humans could provide further knowledge on the feasibility of uterus transplantation and although controversially, it was considered to meet the ethical criterions by the regional ethical board in Gothenburg 2012 (20, 49). After the initial promising results from that study including births (20, 50, 51), at least ten centers have acquired ethical approval for either uterus transplantation with deceased donors, live donors or both, known through personal communication. There is an ongoing debate whether to use uteri from deceased or live donors as there are pros and cons with both methods (52). Besides the fact that so far only uterus transplantations with live donors has resulted in the birth of healthy children, there are also ethical concerns about using a deceased donor as that may affect the donation process

negatively in two ways: Firstly, it may complicate the relatives' decision making for the consent of multi-organ donation. Secondly, it may endanger the quality of the donated lifesaving organs as it may prolong their surgical procurement. The foremost reasons for choosing a deceased donor are the avoidance of all potential maleficence and risk with a live donation and to make the most of the deceased donor organ pool first. In the end, the local experiences, regulations and opinions of the ethical institutions decide on which uterus donor model to implement in a study and eventually in clinical practice. There are now, besides the trial in Gothenburg, ongoing studies with live uterus transplantation in several parts in the world: United States (Dallas) (22), Czech Republic (21), Germany and China, and with deceased donors: United States (Ohio) (23), Czech Republic (21) and Argentina, published in a scientific journal or known by personal communication with the author.

1.2.2 Advantages of live organ donation

Organ procurement from a deceased donor has to be performed acutely to ensure an adequate donor organ perfusion and function as the risk of cardiac arrest is known to increase with time after brain death (53). Brain death induces hemodynamic and hormonal changes as well as an inflammatory response that all together cause morphological and immunological change in the organs designated for transplantation (54). Those changes are related to and further amplified by the ischemia/reperfusion injury (55).

To avoid prolonged treatment that is not of any medical gain for the donor, Swedish regulations state that the procurement has to be initiated within 24 hours after the brain death diagnostics have been performed (56). In contrast, living kidney donation is an elective procedure normally planned months before the surgery. That results in following advantages:

1. **Proper time for organ quality assessment.** The evaluation period allows time for investigation of manifest or occult kidney disease with blood tests, urine analyses, radiology, and clearance measurement to determine kidney function. Several of those tests cannot be performed or analysed acutely (57).
2. **Minimizing risk for transmitting disease.** Although todays' serological tests for transmittable infectious disease are quick and reliable, there is a risk of transmitting bacteria from the deceased donor, as there may be an underlying sepsis. The risk of transferring malignancies is also

higher as the health history of the deceased donor may be unknown and there is usually no preoperative CT-scan (58-60).

3. **Reduction of cold ischemic time.** The live donor nephrectomy and the transplantation are normally performed on the same operation facilities in parallel or consecutively. That reduces the period when the kidney is un-perfused, the cold ischemic time, which is injurious to the kidney, and therefore diminishes the risk for delayed graft function (61).
4. **Optimal timing for transplantation.** Living kidney donor transplantation makes it possible to transplant the recipient pre-emptively, i.e. before the need for dialysis. That affects the long term survival as it decreases with time on renal replacement therapy (30, 62).
5. **Prevailing immunological barriers.** AB0 incompatible live kidney donation, can be performed safely if the recipient is treated pre-operatively with A/B antibody immunoadsorption and anti-CD20 monoclonal antibodies (63). That treatment requires planning and needs to be started several weeks before transplantation.

1.2.3 Results

Kidney transplantation prolongs life for the recipient (30, 62) and considerably improves QoL (64) compared to renal replacement therapy. In terms of kidney function, the results from live kidney donation are superior to the results from deceased donation due to the aforementioned advantages. The expected kidney graft survival for a patient transplanted in 2005 has been predicted to be 8.8 years from a deceased donor and 11.9 from a live donor (65). The results at the Transplant Institute, Gothenburg, are presented in Figure 1.

Infertility has a negative effect on QoL as well as on the quality of relationship with the partner (66). Uterus transplantation pertains to treat uterine factor infertility, which affects 1 in 500 fertile age women (67-70). There are no studies on the impact on well-being of the recipient and partner after the end result: birth of a healthy child. Johannesson et al. reported stable well-being of the recipient couple within the first year after the transplantations in the Gothenburg trial (71). So far five births of healthy children are described in the nine cases performed (51). Although pregnancy has previously been achieved in the case with a deceased donor in Turkey, there are no reports of birth (72). It is difficult to interpret those results due to the low number of uterus transplantations so far. Avoidance of the negative effects of brain death as well as point 1-3 in the previous section, may influence the outcome of uterus transplantation in favor of live donation, although to date there is not enough evidence to support that.

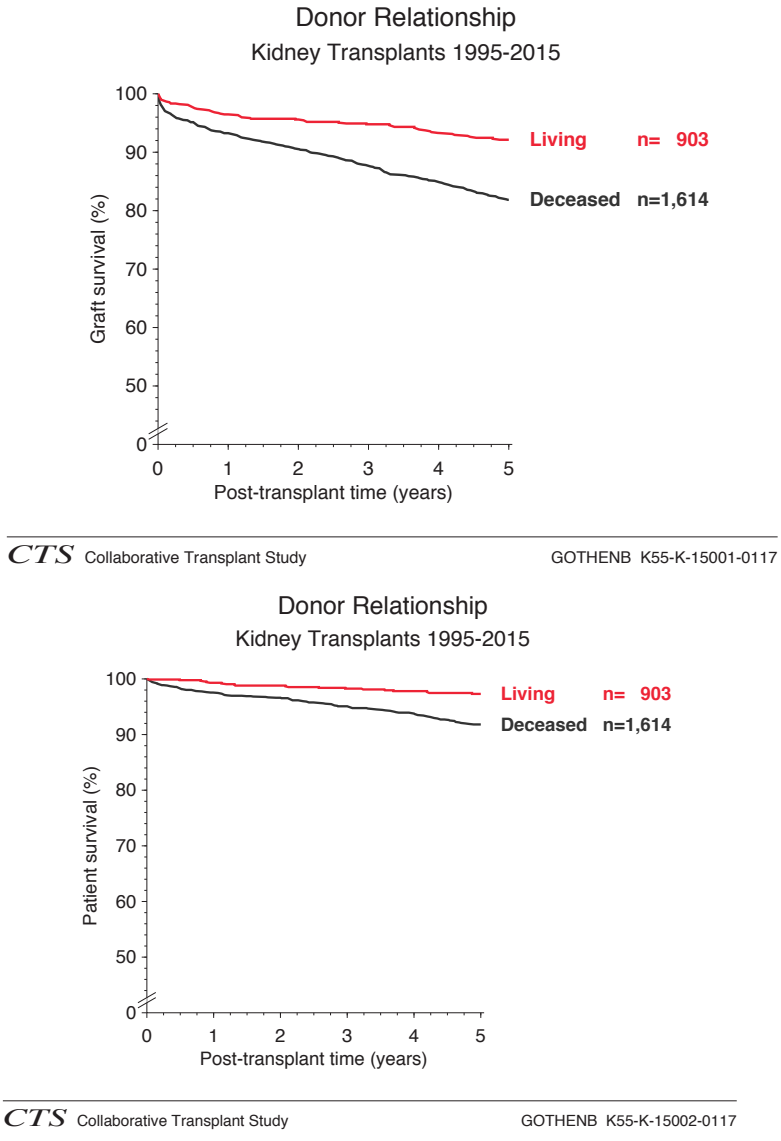


Figure 1. *The kidney graft and patient survival up to 5-years at the Transplant Institute, Sahlgrenska University Hospital, Gothenburg, based on the latest 20-year period in the Collaborative Transplant Study. Grafts from live donors in red and deceased in black.*

1.3 Live kidney donor assessment

In order to minimize the risk for the kidney donor, there is a well-defined pre-operative assessment process to detect any physical, social or psychological risk. The routines for donor assessment as well as criterions for acceptance may vary among different European countries as showed in the EULOD-project (73) and have also changed over time (74). There is a tendency to accept more medically marginal donors by means of hypertension, obesity, high-age and reduced glomerular filtration rate (75). The Swedish national guidelines for kidney donors provided by the Swedish Transplant Society, consider manifest diabetes, BMI > 35 and hypertension as a contraindication although well-regulated hypertension in potential donors over 60 years of age may be considered if there is no sign of end organ damage (76). Those guidelines are consistent with the absolute and relative contraindications suggested by Kher and Mandelbrot shown in Table 1 (77).

Table 1. The table shows absolute and relative contraindications for live kidney donation.

Absolute Contraindications	Relative Contraindications
Age <18 yr	Age 18–21 yr
Mentally incapable of making informed decision	Creatinine clearance <2 SD below mean for age
Uncontrolled hypertension or hypertension with end organ damage	Hypertension in non-Caucasian race
Diabetes	Hypertension in young donor
BMI >35	Prediabetes in young donor
Active malignancy or incompletely treated malignancy	BMI >30
Untreated psychiatric conditions	Microalbuminuria or proteinuria
Nephrolithiasis with high likelihood of recurrence	Bleeding disorder
Evidence of donor coercion	History of thrombosis or embolism
Persistent infection	Nephrolithiasis
	History of malignancy, especially if metastatic
	Significant cardiovascular disease

According to the Swedish guidelines, an acceptable evaluation process for a live kidney donor should span over 3-6 months. The different steps and investigations are summarized in Figure 2. The main principle is to start with a general health screening and to provide full information about risks and results as well as to elaborate on the donor's will to donate exploring potential coercion. Then follow immunologic tests to identify and avoid potential immunologic barriers, lab tests, and finally more advanced clinical investigations, possibly invasive, for donor organ evaluation. Those principles can be applied to all living organ donors.

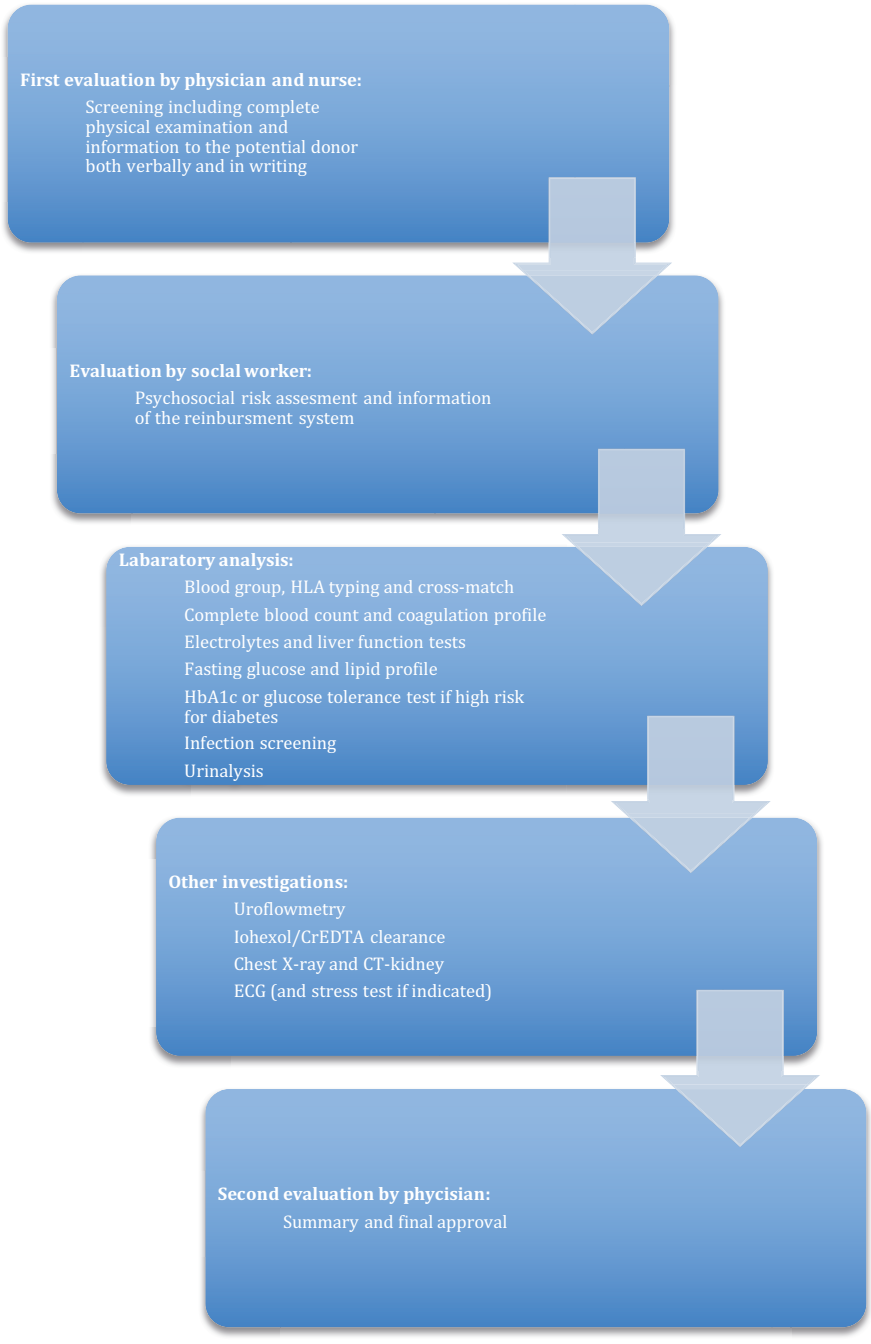


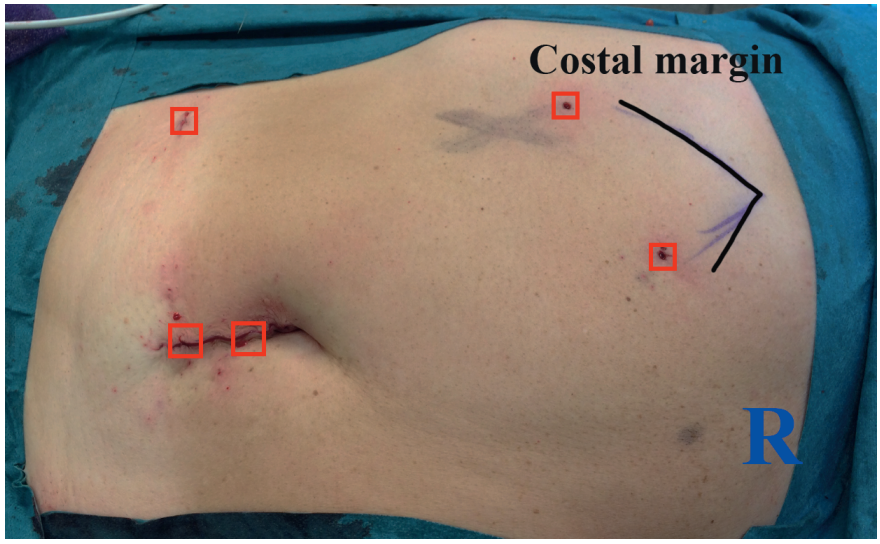
Figure 2. *Flow chart of the evaluation of a potential live kidney donor.*

1.4 Surgical technique

Donor nephrectomy has evolved. During the first decades a flank incision with retroperitoneal dissection, often including a rib resection (78), or a midline transperitoneal approach was standard (79). Dr. Blohmé later described the mini open anterior sub-costal retroperitoneal approach on a supine patient, which was the standard method for many years in Gothenburg (80, 81). That latter approach correlated with less morbidity than the classic flank incision with rib resection (82).

Dr. Ratner performed the first minimally invasive laparoscopic donor nephrectomy in 1995 (83). That method has demonstrated less postoperative pain, shorter hospital stay and faster return to work than the mini-open anterior approach (84, 85). In the early years of laparoscopic donor nephrectomy there were reports of serious complications and loss of grafts but during the last decade the procedure has increasingly been considered as safe as an open procedure (86). The laparoscopic technique was introduced in 1998 in Gothenburg and was the first choice for left kidney nephrectomies until 2013 after which it became the standard method on all donor nephrectomies.

There are several variants of the laparoscopic technique: a hand-assisted intra-peritoneal approach described by Dr. Wolf in 1998 (87), and different retroperitoneal approaches including the retroperitoneal hand-assisted technique described by Dr. Wadström in 2002 (88, 89). The hand-assisted techniques have evolved to shorten the learning curve and further minimize the risk of adverse events and although preferred by some surgeons, the technique has neither shown to be safer, compared to standard laparoscopic, in the meta-analysis by Greco et al. or in a recent randomized trial (86, 90). The true intra-peritoneal laparoscopic technique has cosmetic advantages and is the method of choice at the Transplant Institute in Gothenburg (Figure 3).



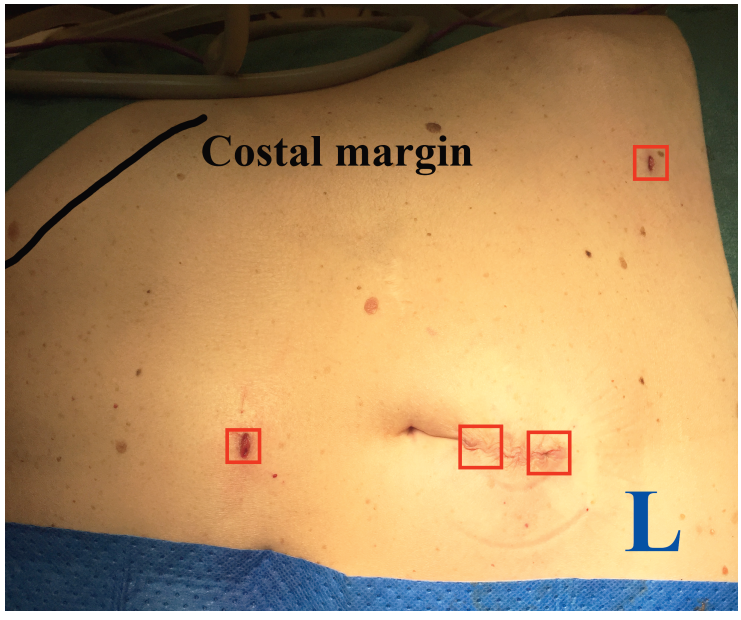


Figure 3. *Standard port sites (red squares) in right (R) and left (L) donor nephrectomy at the Transplant Institute, Sahlgrenska University Hospital, Gothenburg.*

The first robot assisted laparoscopic donor nephrectomy was described by Horgan et al. 2002 (91). The procedures were hand-assisted together with use of the first generation da Vinci Surgical System. Series of fully robotic assisted donor nephrectomies have been published later with comparable safety data (92). The results seem to be equivalent, although more recent studies report shorter length of stay after robot assisted donor nephrectomy when matched to standard laparoscopic procedures (93, 94).

There is only one study published on a series of living donor hysterectomy (20). The procedure was performed via a midline incision from the pubic bone to the umbilicus. The uterus was removed with long vascular pedicles consisting of the bilateral uterine arteries and veins including parts of the internal iliac vessels. Figure 4 shows a schematic picture of the anatomy in the live donor uterus transplantation. The ligaments for fixating the uterus, the round ligaments and the sacrouterine ligaments, as well as a sheet of the bladder peritoneum were preserved on the graft side. The uterine branch of the utero-ovarian vein was preserved. The vagina was transected 10–15 mm caudal to the vaginal fornix. The duration of the procurement ranged from 10-13 h. A group in China has presented a case with donor hysterectomy by robotic assisted laparoscopy with similar duration of surgery although it has not been published in a scientific journal so far.

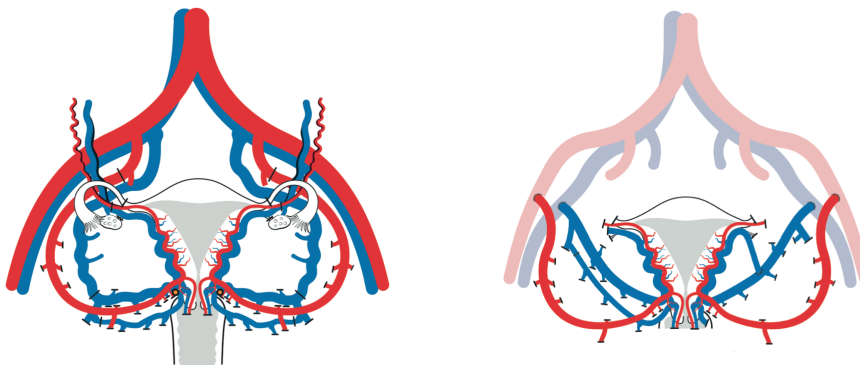


Figure 4. *Above is a schematic picture of the anatomy showing the uterus in donor to the left, and the transplanted uterus in the recipient to the right.*

1.5 Live kidney donor outcome

The overall outcome described by Matas et al. in 2003 of 10,828 kidney donors, indicates a low risk of morbidity and a mortality rate of 0.03%. Ibrahim et al. concludes, in the study on long-term outcome of 3,698 kidney donors, that the mortality rate has changed little during the years despite newer surgical techniques and that the donors have a normal lifespan when compared to the general population (95). However, as stated by Ommen et al.: "absence of proof is not proof of absence". Even if live donation has been performed since the 50's, the long-time follow up is limited as many are lost to follow up and until the 90's the numbers of live donors were relatively limited. The long-term risk is also difficult to assess due to the difficulties in selecting a comparable perfectly healthy control group. When compared to the average population the fact that a live kidney donor lives longer is probably due to that selection (96).

1.5.1. Surgical complications

In the study by Matas et al. reoperations occurred, depending on technique of donor nephrectomy, in 0.4-1.0% of the cases (97). Mjøen et al. reported on a single centers experience of 1022 consecutive donor nephrectomies, and found a frequency of 2.9% reoperations with variations depending on technique and era (98). Reasons for reoperation commonly described are bowel perforation, bowel obstruction, bleeding, deep infection and incisional hernia (97-100).

The rate of complications not requiring surgery ranges from 1-20% in the literature (84, 97-100). They include urinary tract infections, urine retention, chylous ascites, pneumonia, wound infections, blood transfusion, numbness of the thigh, deep vein thrombosis, pulmonary embolism and scrotal swelling.

There are different proposals on how to classify surgical complications of donor nephrectomy (56, 101). Most of those are based on the system of surgical classification by Clavien, modified in 2004 (102, 103). Even if the system proposed by Kocak et al. in 2006 (56) has been used in more recent literature (99, 100) surgical complications are not presented uniformly (84, 98).

1.5.2. Psychosocial outcome

Despite reports of negative outcomes for some kidney donors; lower-quality relationships, depression, anxiety, stress, and a decrease in QoL, the psychosocial health of most donors appears unchanged or improved by donation in the

meta-analysis by Clemens et al (104). A later retrospective multicenter study by Clemens, with a control group, showed similar reassuring results (105).

Short Form 36 (SF-36) (106) is the most frequently used instrument for measuring the psychosocial health in the living kidney donor, although other validated instruments and investigator-developed surveys are also used (104). SF-36 measures self-reported health related quality of life (HRQoL). There are some prospective studies of kidney donors using SF-36 (107-111). They report of an initial decline in QoL after donation but at three months and onward the QoL seems to be the same as before surgery. However, those studies do not include consecutive monthly postoperative measurements.

There are known risk factors for worse psychosocial outcome: poor recipient outcome can result in sorrow and depressive symptoms (112), the quality of the relationship before the donation is related to the outcome of the post-donation relationship (113, 114), and ambivalence of the donor may affect the well-being after the donation (115).

1.5.3 Kidney function

After removal of one kidney in the donor, the total numbers of nephrons are reduced with the half, i.e. diminishing the kidney function by 50%. The post nephrectomy adaption is due to a hypertrophy of the remaining kidney (116, 117), and six month after donation the kidney function has recovered to 72% (118).

In experimental studies with removal of the majority (5/6) of the functional kidney mass, angiotensin II was increased in the kidney causing a glomerular hypertension, a phenomenon that may be injurious to the remnant kidney parenchyma (119). Furthermore, the increased level of angiotensin II may be negative for the function of the podocytes, which are important for the compensatory glomerular hypertrophy. That leads to “remnant kidney syndrome”, which is characterized by proteinuria, systemic hypertension, and the histological features of focal and segmental glomerulosclerosis (FSGS). That phenomenon can occur in humans when the kidney has been previously injured by another process such as reflux nephropathy (120) or obesity (121), and is called secondary FSGS and causes end stage renal disease (ESRD).

Most studies show no excess risk for development of ESRD in kidney donors (122-124). Age and obesity in donors are related to the risk of reduced kidney function as in the general population. Mjøen et al. showed an increased risk of ESRD in kidney donors when compared to a selected control group (125). The results of all those studies (122-125) could be related to the selection of control group as discussed by Boudville et al. (126).

1.5.4. Blood pressure

Several studies including a meta-analysis shows a blood pressure increase of about 5 mmHg five years after kidney donation (127-129). Due to the problem of identifying a perfectly matched control group, the relative risk of developing hypertension is difficult to determine. But there does not appear to be an increased risk of cardiovascular secondary manifestations of hypertension in donors (130, 131).

Previous studies indicate an increased risk of development of hypertension in persons with multiple separate arteries to one or both kidneys (132, 133). The mechanism is suggested to be elevated plasma renin level. Renin is transformed into angiotensin II that increases the blood pressure (134). A substantial part of the potential living kidney donors have that variance as the incidence of more than one kidney artery is estimated to be 28% (135, 136). Studies exist on the implication of multiple arteries in the remaining kidney, but are few (137-139).

1.6 Outcome after donor hysterectomy

In the United States over 600 000 hysterectomies are performed each year (140). Most are for benign indications. A study of more than 4,000 patients who underwent abdominal hysterectomy because of benign disease, reported a major complication rate of 3.6% while minor complications were noted in 2.4% (141). In radical hysterectomies, for malignant disease, a study of 400 cases showed a total complication rate (non-graded severity) of 24% and a mortality of 0.5% (142).

Previous to the study in Gothenburg, Fageeh and co-workers had performed the only live donor uterus transplantation (18). The uterus was removed with a modified technique of vessel dissection. The vessels were however too short for direct anastomoses in the recipient and extension with saphenous veins were necessary on both uterine arteries and veins. The paper does not report the donor outcome after surgery.

In the study by Johannesson et al. in Gothenburg, 19 radical hysterectomies were performed with extensive vessel dissections rendering in the length of 70 mm of uterine artery and 50 mm of uterine veins (45). That was considerably longer than the adjacent vessel lengths reported by Fageeh and there was no increased morbidity when compared to a control group that underwent the same procedure without the modified vessel dissection.

In the literature review by Flory et al., there is some evidence that hysterectomy may cause symptoms related to pain, sexual dysfunction, and psychologi-

cal distress that may affect the well-being (143). However, most patients do not experience any psychosocial impairment and may even report improvement. Depression, anxiety and life stressors may have a negative impact on the outcome of hysterectomy whereas a good quality of partner relationship and adequately sexual functioning may positively influence the outcome.

2. Aims

The principal objective of the thesis was to investigate the outcome for the living kidney and uterus donor both medically and psychologically after donation and to investigate if there are markers indicating elevated risk for the donor. Four specific aims were formulated into the following questions:

1. How is the long-term development of renal function in living kidney donors?
2. Do multiple arteries in the donors' remaining kidney influence the outcome in the first six months?
3. How long does it take to recover after a live kidney donation and what parameters affect that process?
4. What is the medical and psychological outcome after live uterus donation?

3. Patients and Methods

All patients were recruited from the Transplant Institute at Sahlgrenska University Hospital. After verbal and written information was given, a written consent from the participants was obtained in study I, III and IV. Study II was designed as a registry study and as there was no need for any new interventions of the participating population, no written consent was requested (approved by the Regional Ethical Review Board in Gothenburg EPN 058-17). The study populations and study design in each study are summarized in Table 2.

Table 2. The table is an overview of the study cohorts and designs.

	Patients	Method
Study I	573 kidney donors between 1965-2005	Cross-sectional study with analysis retrospectively
Study II	692 consecutive kidney donors between 2000-2013	Retrospective analysis of prospectively collected data
Study III	48 consecutive kidney donors in 2010	Prospective study where participants are their own controls
Study IV	All 9 uterus donors in the 2012-2013 uterus transplantations trial	Prospective study where participants are their own controls

3.1 Kidney function

Kidney function can be measured by the clearance from the blood of certain substances, termed measured Glomerular Filtration Rate (mGFR). In study I and II either iohexol- or Cr-EDTA clearance were used for mGFR as they correlate extremely well (144). Clearance can also be predicted from the level of creatinine using the Modification of Diet in Renal Disease (MDRD) four or six factor formula, termed estimated Glomerular Filtration Rate (eGFR) (145). In study I the four-factor formula was used. Donor kidney function in study I was compared with the expected decrease in GFR in healthy Swedish people, 1 mL/min/year from age 50, as shown by Granerus et al. (146).

Besides mGFR, lab tests for detecting the potential manifestation of chronic kidney disease (147) were collected at the cross sectional follow up in study I: s-creatinine, s-urea, s-albumin, b-haemoglobin (Hb), s-parathyroid hormone (PTH), urine albumin excretion and urine albumin/creatinine ratio.

In study II, mGFR and s-creatinine both pre-operative and at 6 months post-operative, were to be retrieved from the local quality register "TIGER" or from the center responsible for the follow-up.

3.2 Blood pressure

Blood pressures were to be obtained in the medical follow-up performed cross-sectional, study I, or at 6 months, study II. In the latter, it was to be compared with the pre-operative value obtained in the donor assessment. The measurements were performed by indirect method either with the manual auscultatory technique or with an automated electronic manometer. There are sources of error with both techniques as the true blood pressure can only be obtained with invasive intra-arterial measurement (148). Single measurements were used. Treatment with anti-hypertensive drugs, were recorded in all follow-ups.

3.3 Surgical complications

The Clavien-Dindo classification (103) was used for grading the post-operative complications in study II, III and IV. If there was more than one complication in a patient, the highest grade was recorded according to the instructions by Clavien. Any event that deviated from the expected standard recovery was considered a complication.

The method of retrieving data on the complications was slightly different in the studies:

II. Donors' complications were registered at discharge and 1 month by the transplant units' health care professionals. At 6 months, the physician at the referral unit reported to the registry. Standardized forms developed to fit the registry of Scandiatransplant were used.

III. The donor and the recipient data were registered using forms designed by the investigators. The transplant units' health care professionals filled in the forms at discharge, 1-, 3- months and 12-months postoperatively.

IV. The donor complications were registered by the physicians involved in the study at discharge, at the 3 months postoperative clinical evaluation, and at the interview at 12 months with specific questions with focus on symptoms

from the urinary tract and the gastrointestinal system, sensibility disturbances, and scar inconvenience. The recipients' complications were registered continuously throughout the study period.

3.4 Angiography

Pre-donation angiograms were reviewed in study II. Computed Tomography angiograms (CT angiogram), Magnetic Resonance Angiograms (MRA) or conventional angiograms were all accepted. All separate arteries originated separately from the aorta and ending in the kidney were counted.

3.5 Physical activity

The preferred method of measuring physical activity with an accelerometer as outlined by Trost et al. were used (149): Selection of comparable and reliable accelerometer, Yamax Digiwalker (150), hip placement and careful instruction including the recommended and minimum of 3 days of monitoring each week for estimating the weekly activity level.

There are many different validated accelerometers available on the market and even if their accordance varies compared with the gold standard method for energy expenditure, the doubly labeled water method, the method of using accelerometer to assess daily physical activities is still considered reliable (151).

3.6 Patient reported outcome measures

Patient-reported outcome (PRO) measures is defined by the Food and Drug Administration (FDA) as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else." (152). Observational and experimental studies have increasingly included PRO as it is widely accepted that the patient's report is the best source of information about what he or she is experiencing (153). Different domains are used for PRO including symptoms (e.g., pain, fatigue, nausea), functional status (e.g., sexual, bowel, or urinary), well-being (e.g., physical, psychosocial), HRQoL, and satisfaction with the medical procedure. Importantly, in research PRO must demonstrate robust properties such as validity to provide conclusive results in research (154).

In addition to validated PROs the uterus donors (study IV) were asked at the 1-year follow-up if they had returned to their pre-donation mental health, if they had any regrets in case of graft loss, and if they had returned to previous activities both professionally and privately.

3.6.1 SF-36

To study HRQoL in paper III and IV, the Swedish version of SF-36 was used (155). It consists of 36 questions to assess both mental and physical health. The summary score for the mental part (Mental Component Summary [MCS] score) and for the physical part (Physical Component Summary [PCS] score) were calculated based on the formula designed for the Swedish population (156). MCS and PCS scores are mean 50 with a SD of 10, in a normative population (157). The measurements were conducted before surgery and 3, 6 and 12 months after in paper IV, and in paper III before and at 1, 2, 3 and 12 months after donation.

3.6.2 HADS

Hospital Anxiety and Depression Scale (HADS) is a validated instrument to measure depression and anxiety (158). It was used among the uterus donors in study IV pre-operatively and at 3, 6 and 12 months. The scale, developed to include 14 items, measures two dimensions with 7 items each: anxiety (HADS-A) and depression (HADS-D). The norm mean results when tested on a Swedish female population (age 30-59 years), were HADS-A 4.76/21 and HADS-D 3.76/21 (159).

3.7 Socioeconomic factors

Socioeconomic status (SES) is multidimensional and consists of factors such as income, level of education and occupation. Measuring one of those factors as a marker for of socioeconomic status on health is problematic as they are not interchangeable (160). In Europe, occupation is commonly used for stratification (161, 162). In study III the type of occupation was used for dividing the donors into blue/white collar workers or physically/non-physically demanding work. The donors' monthly income was also registered. In study IV the donors occupation was registered as demographic data.

The length of sick leave was registered in study III and IV both to measure socioeconomic and clinical outcome.

3.8 Uterus donor assessment

The principles of donor evaluation as a team effort, with focus on risk minimization as outlined in previous chapter, has been practiced for decades although the guidelines have been updated (74, 163). The process for pre-donation assessment of the uterus donors in study IV was based on the evaluation process for live kidney donors (Figure 1), with additional screening and organ specific evaluation. The potential recipients recruited all the uterus donors. Eleven out of 30 initially interested possible recipients wanted to participate after thorough information. Finally, 9 donor-recipient pairs were selected after assessment.

3.8.1 Uterus donor medical assessment

Lab-tests were used as described in Figure 1 for screening of blood-, liver-, and kidney-disease, diabetes, dysfunction of coagulation and tissue compatibility. The donor and recipient had to be AB0 compatible and no donor specific antibodies were allowed in the recipient. HLA-mismatch was accepted. A chest x-ray and electrocardiography were made and if indicated, a stress test was performed. A cardiologist made the general medical assessment. A gynaecological examination, cervical cancer screen test, and additional MRI and ultrasound were used to evaluate the suitability of the uterus and its vascular supply. The donor had to be in perfect health to be considered for donation.

3.8.2 Uterus donor psychosocial assessment

A prerequisite for a potential uterus donor is to be done with childbearing for own family formation. A psychologist, independent from the psychologist that evaluated the recipients, performed a semi-structured interview to assess the suitability of the donor and to expose and minimize the effect of inherent coercion (164). The interview was focused on psychological well-being, knowledge about the project, risks, ambivalence, and the relationship with the recipients. A social worker with long experience from other living donors made a second risk assessment. As supplementary mental health screening, the validated Swedish

versions of the Psychological General Well-Being Index (PGWB) (165, 166), the Dyadic Adjustment Scale (DAS) (167) the SF-36 and HADS, were used.

The PGWB measures subjective well-being or distress and was first described in 1961, revised to a 22-item tool in 1984, and is considered to be one of the first generic instruments of HRQoL. The global score was used although there are six dimensions: anxiety, positive well-being, self-control, depression, general health, and vitality. The global score of PGWB in a reference group of Swedish women is 100.7 (97.9-103.5), mean (CI) (168). The DAS instrument was used to assess quality of the donors' marital relationship. The instrument has a global scale that consists of four subscales: marital satisfaction, cohesion, consensus, and affectional expression. The mean (SD) value of DAS in a healthy Swedish control group of women was found to be 118.3 (10.6) (169).

3.9 Selection of kidney for donation

There are principles for preoperative selection of a kidney for donation. Each centre has its own selection procedure for minimizing the risk for both the donor and the recipient. At our centre, the left kidney is first choice if there is a single artery, as the normal anatomy will provide a longer graft vein on the left side. In presence of more than one artery on either side, the side with single artery is selected, as it will be easier to anastomose in the recipient. If there is a small caudal polar artery the kidney is rejected to minimize the risk of endangering the vascular supply to the ureter. In presence of two arteries on both sides, the left kidney is selected. A minor abnormality that is not considered to endanger the function of the kidney, including a somewhat smaller size, is accepted for donation i.e. leaving the normal kidney.

3.10 Thrombosis prophylaxis

All donors received thrombosis prophylaxis intra operatively with dextran and postoperatively with dalteparin for seven days in study III, and three weeks in study IV.

3.11 Statistics

Conventional statistical methods were used in study I, II, and III including student’s t-test for comparison between groups, multivariate regression analysis (I)

and analysis of covariance (II). The non-parametric Pitman's test was applied to test correlations between different variables in study I. To study relationships between GFR and current age and time since donation in study I, the GFR values were transformed to into normally distributed. The interaction between age and time since donation was also included in the model and the curves were smoothed using spline functions. In study III, confidence intervals (95%) were constructed using the difference between the baseline values and the values between the different time points of the SF-36 measurements (MCS and PCS). The difference between pre-donation and one month SF-36 was analysed with linear regression models to explore if the drop could be explained by clinical and socioeconomic factors. In order to explore if the time to max number of steps could be explained by the studied clinical and socioeconomic factors a cox regression model was used. The level of statistical significance was determined to $p<0.05$ in study I-III. In study IV, only median and range were used to describe the material, as the analysis was on individual level.

4. Results

4.1 Long-term results for live kidney donors

Out of the potential 1100 donors between 1965-2005, 823 and were asked to participate meeting the criterions of being alive and resident in Sweden. The median age and time since donation of the 573 participants were essentially the same as the 823 and 59% of the donors were women. In the study group, three donors were transplanted or on dialysis. In addition, four of the late donors were found in the Swedish Renal Registry diagnosed with ESRD.

4.1.1 Kidney function improved with time after donation

There was a negative correlation ($p < 0.001$) between age and mGFR. Urea and creatinine increase with age, as there were positive correlations between age and s-urea ($p < 0.001$) and between age and s-creatinine ($p < 0.001$). The opposite correlations were found between mGFR, s-urea and s-creatinine and time since donation ($p<0.05$), i.e. mGFR increases with time after donation and urea and creatinine decreases. A model of the mGFR development is shown in Figure 5.

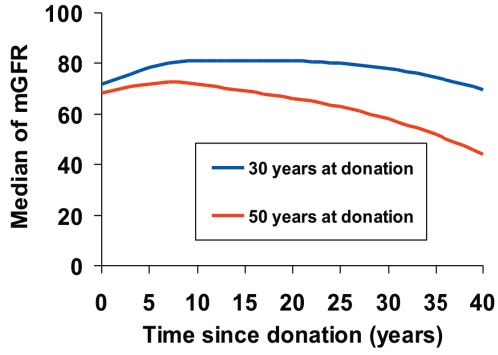


Figure 5. The illustration of a model of the evolution of mGFR on a 30 and 50-year-old donor at time of donation.

4.1.2 Blood pressure and u-albumin increased after donation

Blood pressure increased with time to donation and age ($p<0.05$). In the study cohort, 23% of the donors were treated with antihypertensive drugs and 22% had over 140/90 mmHg in blood pressure at the medical check-up, where the mean donor age was 62. The level of urine albumin excretion ($p < 0.001$) and albumin/creatinine ratio ($p<0.008$) increased with time since donation although no correlation with actual donor age was found.

4.1.3 Hb and PTH were correlated to GFR

There was a strong positive correlation between Hb and eGFR ($P < 0.001$). Lower eGFR correlated with higher PTH ($p < 0.05$) and 20% of the donors were above the recommended upper reference PTH limit of 6.90 pmol/L.

4.1.4 Hb and albumin decreased with age

There were 12 anemic donors (2.1%) by definition of the corrected Nilsson–Ehle results for elderly people (170). Regression analyses revealed a negative correlation between Hb and age ($P < 0.001$). In total, 22 (4.3%) of the donors had values below the reference level of s-albumin (36 g/l). The level of s-albumin decreased with age ($p<0.05$).

4.2 Outcome of donors with >1 kidney arteries

Between 2000-2013 there were 692 live kidney donations. The median donor age was 49 and 60% were women. More than 30% had kidneys left with multiple arteries. There were complete follow-up data on the majority of the donors. The values of pre-donation study factors age and sex where distributed similar in both the whole group as in the subgroup with complete data. Further, age and sex where comparable between the two groups intended for analysis; multiple arteries in the remaining kidney and single artery in the remaining kidney.

4.2.1 Few donors had surgical complications

Less than 10% had a registered surgical complication and less than 1% had to be re-operated (Table 3). The complications were all well known for the procedure.

One donor was diagnosed with pulmonary embolism. There was no need for intensive care or any deaths within the study period.

Table 3. Surgical complications in study II and III that needed re-operation, 0.9%.

	Incisional hernia	Peritonitis	Herniation in trocar site
Number of donors	5	1	1

4.2.2 Kidney function decreased after donation

There was a raise in s-creatinine levels 6 months after donation ($p<0.05$). A corresponding drop in mGFR ($p<0.05$) was detected. The mean BP did not increase, but there were some values above the limit of hypertension (140/90 mmHg) in the follow-up. No statistically significant difference was detected between the groups of single/multiple arteries.

4.3 Recovery after kidney donation

The study cohort consisted of 48 consecutive living donors in 2010. The median donor age was 47 and 71% were women. The donors stayed in hospital for median 6 days. There was one complication greater than Clavien grade II. That donor had to be re-operated after which the recovery was uneventful (Table 3). There were no thromboembolic events. Twenty-one of the procedures were performed with the mini open anterior technique and 27 were laparoscopic.

4.3.1 The donors were workers

Only one donor was unemployed at the time of donation. The majority of donors had a physically demanding work. The self-reported median income of the donors were in concordance with the income of the Swedish general population in 2010 (171). The median and mean sick-leaves were consistent, but there was one donor with a considerably longer sick-leave that was related to general symptoms not requiring any medical treatment.

4.3.2 Physical activity after donation gradually increased

The number of steps registered in the donors varied between individuals as well as between different measurements in the same donor. The collected data on the donors' registered number of steps, showed a gradual increase in the of number of steps although time to the maximum number of steps was diverse. Data were missing from 21 donors for unknown reason. Figure 6 show an example of one participant's registered steps (normalized curve) and SF-36 at different time points.

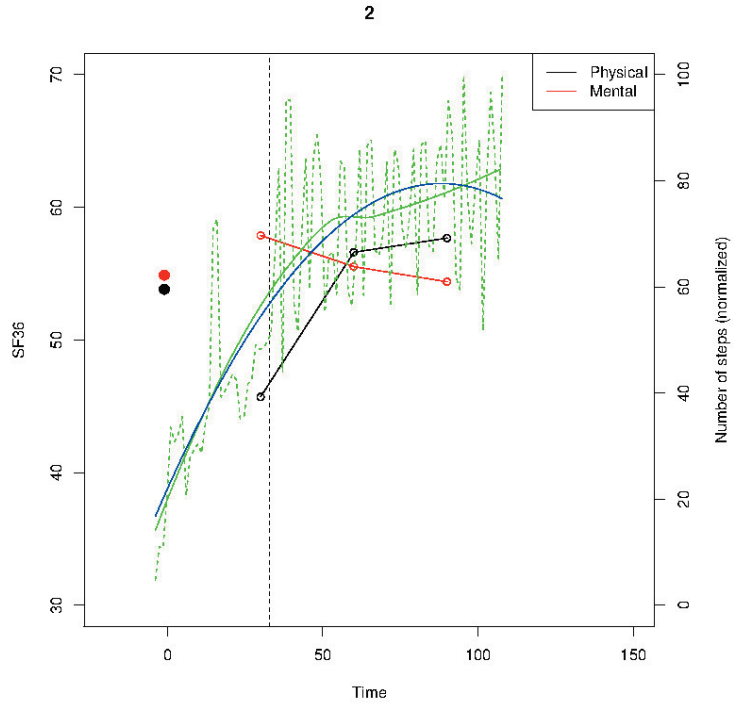


Figure 6. The normalized curve (blue line) of number of steps and the SF-36 PCS (Physical Component Summary score) and MCS (Mental Component Summary score) in subject 2 in the study on recovery after donor nephrectomy. The number of steps increases until three month after surgery.

4.3.3 The reported QoL returned to pre-donation levels

The mean MCS and PCS were both 53 before donation. The scores dropped at the one month measurement (CI 95%) and gradually increased to mean values of the norm population (172), or over. MCS, the mental component, was back to pre-donation levels at two months and PCS, the physical component at three months. The drop of PCS was related to income and physically demanding work ($p<0.05$). Between 3 and 12 months, two donors dropped over 2 SD in PCS and MCS.

4.4 One-year outcome after uterus donation

Nine cases of live uterus donation were performed 2012-2013. The donor surgery had duration over 10 h. There were perioperative autologous blood transfusions in two cases, but no need for allogenic transfusion. The donors all stayed at the hospital for the planned 6 days. The median sick-leave was 56 days. Donor 8 had a prolonged sick-leave for 132 days.

4.4.1 Serious complication in one donor

Only three complications were registered in the series. Two were transient Clavien grade I: nocturia and unilateral sensibility impairment of the thigh (Meralgia paraesthetica). Donor 2 had a Clavien IIIb complication, where one ureter had to be re-implanted after a period of a conservatively treated ureteric-vaginal fistula. That complication required in all 29 days of hospitalization.

4.4.2 The donors had good psychosocial health before surgery

The global score of PGWB was within or higher than the values of a healthy reference population of women between 50-60 years (168). No donor had lower DAS then -1 SD of the reference values in a healthy Swedish control group (169). All donors were within mean +/- 1 SD of the normative Swedish population of the SF-36 PCS/MCS dimensions (156). Only one donor was over 1 SD (HADS-A) of the reference value of HADS in a Swedish population of women 50-59 years old, indicative for anxiety. The psychological interview revealed fear of the surgical procedure but strong determination to donate. The rest of the donors had below or within mean +/- 1 SD of norm values. The interviews were

consistent with the findings in the test instruments and showed low psychosocial risk. A summary of the results from the tests is presented in Table 4.

Table 4. Values of self-reported psychosocial health among uterus donors before donation and norm values in the Swedish population.

	PGWB	DAS	PCS MCS	HADS-A HADS-D
Uterus donors[1]	121(100-125)	130 (112-140)	56.7 (44.7- 58.1) 54.9 (47.4-58.6)	5 (0-12) 0 (0-4)
Norm population	100.7 (97.9-103.5)[2]	118.3 (10.6)[3]	50 (10)[3]	4.72 (3.86)[3] 4.45 (3.83)[3]

[1] Values in median (range)
[2] Mean (CI 95%)
[3] Mean (SD)

4.4.3 Events in the recipient

Two grafts had to be removed during the study period: one on day 3 (recipient 9) and the second on day 105 (recipient 2). In addition, there were a total of 10 rejection episodes in 5 of the remaining 7 recipients during the first year. In 5 of those episodes the recipients were admitted to hospital for treatment. No other serious event occurred.

4.4.4 Return to baseline psychosocial health after donation

Although there were recorded drops in the SF-36, there were no need for psychological or psychiatric counseling for the donors and the results in HADS were below the cut off [7] for anxiety and depression during the follow-up (158). They reported to have returned to their pre-donation habitual social and physical activities as well as working tasks. Besides the graft hysterectomies in the recipients, there were records of other stressful life events during the study period. Donor 2 suffered from a serious complication and the recipient, her daughter, lost her graft. That donor was in hospital at the time of the 3 months follow-up and she did not return the SF-36 or HADS questionnaires at that time-point. At 6 months, her SF-36 was below 1 SD of the norm. Donor 8 reported MCS below 1 SD of the norm at 12 months. All other PCS/MCS measurements were within mean +/- 1 SD of the norm.

5. Discussion

Both measured and estimated kidney function, in study I, increased over time after donation -compensating for the age related decline which is expected to be 1 ml/min/1.73m^2 (146). That is illustrated with the model for the typical donor at age 30 and 50 in paper I. The finding is consistent with the study by Ibrahim et al. (122). However, both studies are based on large cross-sectional single measurements extrapolated longitudinally. There are also relatively few donors below 30 and over 60 years of age in both studies. That results in increased level of uncertainty when estimating the evolution of kidney function in both younger and older donors. Longitudinal data from the Swiss Donor Registry with repeated measurements of s-creatinine on kidney donors 1, 3, 5 ,7 and 10 years after nephrectomy, shows an initial increase in creatinine after which the level decreases for up to 7 years (173). That also indicates an increase in kidney function for several years after donation. There is a more recent study by Lenihan et al. with a detailed long-term follow-up in 21 live kidney donor including mGFR before, early, (median 0.8 years) and late (median 6.1 years) after donation (174). The result was in concordance as mGFR remained the same between early and late measurements. Furthermore and importantly, they showed that the increased kidney function due to hyperfiltration sustained by increased renal plasma flow as described by Krohn et al. (175), were maintained for 6 to 8 years after donation with no definite contribution from glomerular hypertension.

There were three donors on dialysis or transplanted for ESRD in the study population (I). One became uremic due to cancer in the remaining kidney. That is not related to the donation although the consequence of that diagnosis may have been different if there were two kidneys remaining. One was diagnosed with nephrosclerosis of unknown cause. That diagnosis could hypothetically be related to kidney donation by the mechanism known as the *remnant kidney phenomenon*, described in an experimental research model where 5/6 of the kidney mass is turned ischemic (176, 177). That induces injury to the remnant kidney mass by glomerular hypertension and injury to the podocytes and result in a histological feature of focal and segmental glomerulosclerosis (FSGS). However, as described by Lenihan, there is no evidence of such a mechanism in the live kidney donor (119, 174). The prevalence of 0.5% (3/573) ESRD in the study group (I) compared to the overall 0.1% in the Swedish population, may be explained by the age distribution as the incidence of renal replacement therapy increases con-

siderably between 55-85 years (178) and the donors were aged 61.7 in mean (SD=12.0). The lack of control group in study I makes it difficult to estimate the relative risk of ESRD for living donors. The study of Mjøen at al. of 1,901 kidney donors at a single centre, reported nine donors (0.47%) with ESRD (125). Compared to a control group the risk of ESRD was considerably higher for kidney donors (HR11.38 $p<0.001$). As the reasons for ESRD in that study were mainly immunological diseases (7/9) and diabetes (2/9), which are not related to kidney donation, the mechanism for the increased risk is not clear. The donors who developed ESRD were all related to their recipient and hereditary factors may be the underlying explanatory factor as discussed by the authors i.e. the study provides no convincing support that kidney donation should increase the risk for developing ESRD.

The increase in blood pressure related to time after donation in study I is consistent with the result from the study with matched controls by Garg et al. where they found a HR of 1.4 (129) as well as the meta-analysis paper by Boudeville et al. (128). There was no increase in blood pressure within the first six months post-donation in the whole study population in paper II. A rise in 5 mmHg after donation is seen first after five to ten years (128). Hence, a slowly continuous process may not have been detected after six months. Importantly, no difference was detected *between* the groups of single artery and multiple arteries. Evidence of a higher blood pressure among the donors with multiple arteries would have supported the findings of Glodny et al. (132). However, the outcome of study II is consistent with the long term results in the study by Rizzari et al. and Fehrman et al. (137, 139) and the intermediate-term result by Ma et al. (138), showing no evidence of a raise of blood pressure due to multiple arteries. The mechanism for at systemic increase in blood pressure -as described by Glodny et al. (133), is an increase in renin resulting in a higher level of angiotensin II which by several means increase the blood pressure. A lack of evidence for a systemic effect does not exclude an effect in the glomeruli. A higher level of angiotensin II is injurious for the glomeruli as previously described. There was no proof of damage to the kidney related to multiple arteries as the s-creatinine and the mGFR development were the same in both groups in study II. That is in concordance with previous studies (137-139) although they report on eGFR which is a less accurate measurement of kidney function when GFR is >60 (179). Analysis of urine albumin may have provided indication of glomerular damage but unfortunately that was not included in study II. In the report by Rizzari et al., proteinuria was analysed but the definition used, “any positive result on urinalysis throughout post-donation follow-up”, may have been too wide to detect a relevant difference.

The clinical significance of the increase of microalbuminuria in donors with time after donation in study I (122, 180) may not have been fully investigated. Microalbuminuria may be associated to with an increased risk of cardiovascular disease (181). However, studies on the risk of developing cardiovascular disease in donors show different results and have limitations mainly due to the difficulty in selecting a healthy corresponding control group (125, 131). Surveillance-bias may further contribute to the problems of interpreting the data as live donors in general attend more frequent routine medical check-up due to follow-up programs after donation (129, 131). The studies (I, II) in the thesis were not designed to explore the relationship between the risk for death or cardiovascular disease and the findings of microalbuminuria in donors. Further studies on that are needed.

The physical well-being (PCS) after kidney donation was more affected than the mental (MCS) and donors also recovered slower physically according to the result in study III. To our knowledge, study III is the first prospective study of monthly collected SF-36 up to three months after kidney donation. There is a strength with the use of summary scores to analyse SF-36 as it increases the power and hereby reducing the number of necessary respondents (157). It further improves the simplicity as it involves only analyses of two factors instead of eight. The primary endpoint was to establish when the summary scores were back to the pre-operative levels within an adequate donor group to detect a clinical important difference (CID) defined as 0.5 SD =5 (182). However, there is no previous definition on what a CID is for PCS and MCS in live kidney donors and previous studies on other patient groups report different CID depending on diagnosis. To determine a threshold is of importance for power calculation (157) but may be misleading when presenting the results as discussed by Hays et al. (183). The concluded time to recovery of QoL in study III is however reasonable when using 3-5 as the threshold of CID as suggested by Samsa et al. (182). There was no observed difference at one month in SF-36 between the donors after minimal-open surgery and laparoscopic surgery in contrast to previous studies (107, 111). That may be explained by the impact on the subscale of bodily pain as described by Andersen et al. (111) may not have been revealed in the analysis of PCS. Those studies (107, 111) also included more donors and were randomized. The analyses (study III) to determine the relationship between the initial drop in SF-36 and different explanatory factors may be unreliable as there are relatively few respondents. Those analyses should thus be cautiously interpreted. Study III, is however unique as the relationship between socioeconomic factors and recovery are studied prospectively for the first time. The results of the SF-36 drop being related to both physically demanding work and income

may be explained by the fact that those two factors are not independent of one another i.e. they are correlated.

It is challenging to retrieve data on all items in a PRO instrument and sometimes the respondent fail to report at one occasion which altogether frequently result in missing data in such studies (184). In study III a missing item in SF-36 is treated with list wise case deletion of that respondent as in the study by Andersen et al. (111), more or less assuming that the data is missing completely at random (MCAR). Given the fact that missing data of a specific variable in psychological research often is near random (185) the relationship with other variables may need to be tested to strengthen the assumption of MCAR although confirmation of true MCAR might be impossible (186). Furthermore, case deletion of missing data in health related QoL questionnaires is by other authors considered obsolete and a more appropriate strategy may have been to impute data by a correct technique (187, 188).

The long-term QoL (12 months) when measuring SF-36 and HADS in the uterus donors (study IV), and SF-36 in the kidney donors (study III), indicated return to the well-being measured before donation. That is in line with other studies with long term QoL follow-up of living kidney and liver donors (189-192). The pre-operative measured psychosocial health was in the level or slightly above the average population in both study III and IV which is consistent with previous studies of living organ donors (104, 193, 194). That is probably due to the selection process previously described were psychosocially unhealthy potential donors are declined. PCS and MCS median levels were comparable for the uterus donors and female kidney donors at pre-donation, 3 and 12 months (55+/-2). There were however individual drops in SF-36 among the uterus donors that may be related to the donation process. Psychosocial complications as depression, anxiety, and family relations have been described in previous studies although most living organ donors have positive experiences of the organ donation process (104, 115, 193-197). A recent study by Meyer et al. on long-term experiences of live kidney donors with qualitative in-depth interviews conclude that the donors seem to possess resilient qualities that enable them to address both expected and unexpected long-term consequences (198). To determine whether a significant drop in SF-36 is related to the donation or other life events requires a detailed knowledge of other potential psychosocial stressors. In study IV, uterus donor 8 had other life-events, which could explain her decrease in mental well-being whereas in the case of donor 2, the decline was considered to be related to the undesirable outcome for both her and the recipient. The loss of graft in the recipient may cause depressive symptoms in the donor (112) and although not diagnostic from the HADS-D in donor 2, there is reason to assume that her daughter's graft loss caused a mental strain.

There is no psychometrically validated donor specific questionnaire and as a consequence there is no generic instrument in the Swedish language. That impose difficulties to produce validated research results on donor specific matters such as received information about donation, stresses related to donation, relationship to the recipient, and regret. To cover those issues questions could be systematically asked (199), semi-validated instruments could be developed (200, 201), or qualitative methods may be used (195, 198). Both study III and IV were focusing on generic instruments, however especially in the study of uterus donors, a systematic complementary collection on donor specific topics would have provided more important information. That will be included in the future long-term follow-up studies of the cohort as well as in the coming uterus trial with robot assisted donor surgery.

The time to maximum number of steps registered with a pedometer in the study of the recovery process of kidney donors, may be included in a mathematical model to assess other variables influence on the recovery (III). In study III, which is the first in literature of registered physical activity on live donors, the time to maximum number of steps and also the display of measurements over time varied considerably between donors. Therefore, it was problematic to conclude on a typical pattern. That may require more participants and also less missing data. In order to avoid missing data an application in a smartphone may be used in future studies (202). Although not developed for measuring physical recovery the use of SF-36 seems to be an adequate method as several studies including study III reports relatively consistent findings as previously discussed. A tool more recently developed and validated specifically for measuring the post-operative recovery, the Post-Operative Recovery Profile (PRP) (203), may provide more information on the recovery of donors in the future.

There was one serious post-operative complication, donor 2, graded as Clavien IIIb, in the first study on live human uterus donors (IV). It was an injury to the ureter that resulted in a ureterovaginal fistula and the ureter had to be re-implanted. In the first reported case with live donor hysterectomy, there was a ureteric laceration corrected during the surgery (18). Injury to the genitourinary tract is a known complication to benign hysterectomy and occur with an incidence of 1-2% (204). When performing a live donor hysterectomy, the dissection is far more extensive near the distal ureter in order to preserve the uterine vessels. Although the retroperitoneal space was reported to be extremely inaccessible for unknown reason in donor 2, it is reasonable to presume that the incidence of injury to the ureter will be greater among live uterus donors than found among other indication for benign hysterectomy. The extensive retroperitoneal dissection close to the pelvic vessels and bladder, may have accounted for the two spontaneously resolved complications, nocturia and unilateral sensibility im-

pairment of the thigh. There was no complication outside of the operative field, such as a thromboembolic- or cardiopulmonary- event, despite prolonged surgery. In study II and III, there were in total 0.9% serious complications graded as Clavien III or more and they were also related to the operative field: incisional hernia (=5), peritonitis (=1) and herniation in trocar site (=1). Both the reasons and frequency of grade IIIb complications are consistent with the literature (97-100). One pulmonary embolism was found (II) and no recorded event of deep vein thrombosis (DVT). Other studies show 0.02-0.2% occurrence of DVT (97-99). In a prospective study by Biglarnia et al. on thromboembolism after live kidney donation, when a similar prophylactic regime as in study II-IV had been used, 129 donors underwent post-operative duplex investigation (205). They reported detection of DVT in one donor, and suspected DVT in additionally two cases (0.8-2.3%), all asymptomatic. The low rate of thromboembolic event in study II-IV, may be due to missed diagnose or unreported event in the registry (III). However, there seems to be a low risk due to successful pre-operative screening and successful prophylaxis. The benefit of post-operative screening for DVT is debated and there is little evidence to support such a program for patients at low risk as the live kidney donors (206). It may however be indicated in high risk groups. Prolonged surgery time may increase the risk for DVT (207, 208) and post-operative duplex of the donors' deep veins in the lower extremities, is included in the new clinical uterus trial.

When the number of events that occur is small in relation to the frequency of occurrence of the outcome of interest the study have a risk of being underpowered (209). Therefore, as the frequency of surgical complications in live donors is low, a study designed to investigate the relationship of different variables with donor complications is likely to be underpowered. Other important factors, as by whom and how the complications are registered (210, 211) may influence and bias the results. Due to that, there has to be carefulness in concluding on the calculated relationships of the secondary hypothesises on complications and recovery in study III. The total registered complication rate was different in study II-IV. The methods for retrieving information on the complication were diverse. It is known to be a problem with underreporting in quality registers (211) and there is reason to believe that many minor complications were not reported in the ¨TIGER¨ registry in study II. In study III, an effort was made to detect all complications and both physicians and nurses had to report every event that deviated from an impeccable recovery and standard of care. That resulted in numerous of reported grade I events, that would not have been detected in study II or IV. In study IV, complications noted by the initiated study doctors were registered and minor complications may not have been fully noticed. Donors in need of reoperation or other serious complications, would have been referred back to the trans-

plant centre. Hence, grade III or higher Clavien would likely have been discovered in all three studies. The low number of those serious complications indicates suitable donor selection and perioperative protocols including surgical method for minimizing the risk in study II-IV. Furthermore, the implementation of a similar protocol and guidelines as used for kidney donors on the new group of live donors, the uterus donor, were feasible and safe.

6. Conclusions

1. Renal function improves for several years following donation irrespective of gender and age at the time of donation. After those years, there is a progressive decrease in the elderly kidney donor as the kidney function reduces with age.
2. The number of arteries in the remaining kidney does not seem to influence the live kidney donor outcome.
3. The recovery takes up to three months after kidney donation and socio-economic factors may influence the initial decrease in well-being after surgery.
4. The results in the first study on live uterus donors indicates that the concept is generally well tolerated, both medically and psychologically with return to pre-donation levels of well-being.

7. Future Perspective

The efforts to expand the number of deceased donor organs by legislation, education and optimizing the use of marginal grafts as well as the development of programs with donation after circulatory death, have the potential to increase the number of available organs. But, as the need for organs is increasing, grafts from live donors will continue to contribute substantially to the number of transplantations. In the new field of uterus transplantation, it is difficult to predict if live donors will continue to provide the majority of transplanted uteri. So far, 80% of the performed uterus transplantations have been with live donors.

The live donors are an altruistic group of patients thus it is of major importance to continue the efforts to minimize their risk in the donation procedure. In the thesis, several potential risks are addressed that need to be explored further. Among those are the debated long-term mortality and ESRD among kidney donors. Those issues will be studied on a large population of live kidney donors in Sweden in a new study led by Dr. Ingela Fehrman-Ekholm.

The recovery of live donors should be uneventful and quick so that they can return to their previous working tasks and ordinary daily living as soon as possible. New surgical technique with robot assistance in live kidney donor surgery may further improve the recovery as presented in a recent randomized study by Bhattu et al. (93). There will be more data in the future when analysing the increasing number of procedures performed with that technique at multiple centres. The coming uterus transplantation trial in Gothenburg, with the world's first series of robot assisted live donor hysterectomies, will give important knowledge on the possible benefits with minimal invasive surgery for the uterus donors.

The use of specially designed PRO questionnaires to measure recovery after surgery as the instrument PRP, may be useful in new studies (203). Furthermore, implementation of optimal perioperative care, as seen in colorectal patients with the ERAS concept (Enhanced Recovery After Surgery), may assist in minimizing the time to full recovery as well as reducing the risk for complications (212). Important parts in the ERAS concept; short preoperative fasting, minimal invasive surgical technique, preventing and treating postoperative nausea, and early mobilization, can be applied on the majority of live donors.

Developing and using donor specific questionnaires for both kidney and uterus donors in future studies may better describe and detect psychosocial complications. A prospective outcome study of donor specific issues comparing uterus

and kidney donors, is probably also feasible as most kidney donors are female and at the same age as the uterus donors which facilitate pairwise matching.

Acknowledgement

Firstly, I wish to thank all my great colleagues and co-workers at the Transplant Institute, Sahlgrenska University Hospital, for being supportive in all aspects in completion of this thesis. I especially want to thank:

Michael Olausson, my main supervisor, for guidance and trust in me throughout the project.

Ingela Fehrmam-Ekholm, my co-supervisor, for engaging me in the field of living kidney donation and for initiating this research project.

Annette Lennerling, my co-supervisor, for your devotion and hands-on support. Without you, this thesis would not have been completed.

Markus Gäbel, my colleague, greatest friend and co-donor surgeon, for always boosting me.

John Söfteland, my colleague, friend and co-donor surgeon, for the work on paper III and all other common projects. I owe you particularly for all the proof-reading of my work.

Liza Johannesson, co-worker in the uterus project and friend, for your support in work and life.

Mihai Oltean, my colleague and friend, for the guidance in my PhD project.

Per Lindnér and Lars Mjörnstedt, head and vice head of the Transplant Institute, for supporting my clinical work and research projects.

The whole uterus team led by Mats Brännström, for inviting me to participate in an exciting and successful project.

Finely and foremost my family, Sandra, Svea and Filippa. You fill my life with the deepest love.

The thesis was supported through the ALF agreement, and by grants from the Jane and Dan Olsson Foundation for Science and the Swedish Research Council.

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Appendix

Paper I-IV